In Capsule Series

1st Edition

HEMATOLOGY

Internal Medicine

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INTRODUCTION

Blood consists of :

- Red blood cells (RBCs) .
- White blood cells.
- Platelets.
- Plasma.

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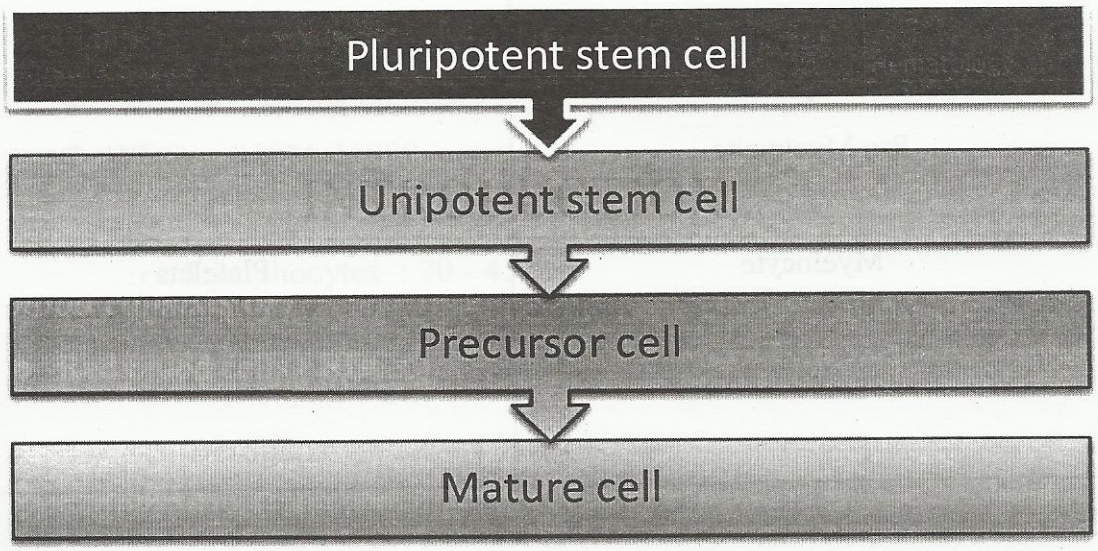
Hemopoiesis

(The formation of blood cells)

- The hemopoietic system includes the bone marrow, liver, spleen, lymph nodes and thymus.
- Liver & spleen are the chief sites of hemopoiesis from 6 weeks to 7 months , when the bone marrow becomes the main source of blood cells. The bone marrow is the only source of blood cells during normal childhood and adult life.
- RBCs survive 120 days, platelets around 7 days but granulocytes only 7 hours.
- **Steps of hemopoiesis :**



Erythropoiesis :

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Pluri-potent stem cell
↓
Uni-potent stem cell (CFU - E)
Colony Forming Unit - Erythrocyte
↓
Pro-Erythroblast
↓
Basophilic Erythroblast
↓
Polychromatic Erythroblast
↓
Orthochromatic Erythroblast
↓
Reticulocyte
↓
Erythrocyte (Mature RBC)

Precursor cell

Granulocytopoiesis	Thrombocytopoiesis
Pluri-potent stem cell	Pluri-potent stem cell
↓	↓
CFU - G	CFU - Mega
↓	↓
Myeloblast	Megakaryoblast
↓	↓
Pro Myelocyte	Megakaryocyte
↓	↓
Myelocyte	Platelets
↓	
Granulocyte (PML)	

Normal ranges (adults)

- Hemoglobin :
  - 13.5 – 17.5 gm /dL (♂)
  - 11.5 – 15.5 gm /dL (♀)
- Haematocrit (PCV): the volume of packed RBCs in 100 ml blood
  - 40 – 52 % (♂)
  - 36 – 48 % (♀)
- RBCs indices :
  - MCV *(Mean Corpuscular volume)* : 77 – 95 fL

    $= \frac{PCV \times 10}{RBCs\ count\ /cmm} = \frac{45 \times 10}{5} = 90$ femtolitre.
  - MCH *(Mean Cell Hb)* : 27 –32 pg

    $= \frac{Hb \times 10}{RBCs\ count/cmm} = \frac{15 \times 10}{5} = 30$ Picogram
  - MCHC *(Mean Cell Hb Concentration)* : 32 – 36 gm/dl

    $= \frac{Hb}{PCV} \times 100 = \frac{15 \times 100}{45} = 33$gm/dl
- RDW (*Red Cell Distribution Width*) : 11.5–14.5%

  RDW is a measure of the degree of **anisocytosis** (variation in RBC size).

  Increased : Many types of anemia (iron deficiency, pernicious anemia , folate deficiency, thalassemia), liver disease.
- Reticulocytes : 0.5–2.5 %
- ESR : 2–12 mm/1st hour .
- WBC : 4000 –11000 /cmm.
  - Neutrophils : 50 - 70 %
  - Lymphocytes : 20 - 45 %
  - Eosinophils : 1 - 5 %
  - Monocytes : 3 - 7 %
  - Basophils : 0 - 1 %
- Platelets 150,000 – 400,000 /cmm.

ANEMIAS

Anemia Scheme

Definition:

Reduction in one of the following parameters :

- RBCs count → N : 4.5 - 6 million\cmm in ♂.
- Hb concentration → N : 15 gm % (13.5 - 17.5) in ♂.
- hematocrite value (*packed cell volume*) → N : 45%

NB

Females are usually 1 to 2 gm Hb & about one million RBCs per cmm less than males. (*due to the effect of androgen in ♂ plus the effect of menstruation*)

Pathophysiology : 4

1. Hyperdynamic circulation → short circulation time & high cardiac output .
2. ↑↑ Erythropoietin by the kidney → ++ RBCs
3. ↑↑ O2 delivery to the tissue (shift of O_2 dissociation curve to the right) : This is due to excess production of 2,3 DPG (*2,3, diphosphoglycerate*) which make the binding between O_2 & Hb very weak.
4. Redistribution of the blood : blood is shifted to the vital organs e.g. brain.

Clinical picture : 4

Symptoms: (*depend on the rate of reduction rather than the absolute value of Hb*)

1. General : Fatigue & lassitude.
2. CVS : manifestations of **low cardiac output** inspite of high Cop.
3. CNS→ loss of concentration , headache & dizziness.
4. Genital : Impotence , menstrual irregularities.

Signs: 4

1. **Pallor.**
2. Hyperdynamic circulation : Tachycardia , ↑S1 , gallop, hemic murmur.
3. lower limb edema **"due to hyperdynamic circulation , hypoxia & heart failure "**
4. papiledema and retinal hemorrhage due to ↑ permeability.

Investigations: 4

Anemia is not a diagnosis, it is an abnormal clinical finding requiring an explanation for its cause.

I.CBC :

- RBCs & HB → ↓↓with all types ☺
- WBCs & platelets → ↓↓ with Megaloblastic , Aplastic anemia
- Indices :
  - MCV, MCH, MCHC : e.g.
    - Normal in hemolytic & aplastic anemia.
    - ↓ in iron **deficiency** anemia.
    - ↑ in **megalo**plastic anemia ***except*** MCHC is normal

II.Color index = 1 (0.9 - 1.1) ☺ ***except***

- Iron **deficiency** anemia < 1
- **Megalo**plastic anemia > 1

III.Bone marrow examinations :

e.g. Erythroid hyperplasia in iron deficiency , aplasia in aplastic anemia …..

IV.Hepatic and renal investigations e.g. KFTs , LFTs.

Treatment: 4

1. Blood transfusion.
2. packed RBCs
3. Treatment of the cause e.g.
   - Fe → in iron deficiency anemia.
   - Folic acid & vitamin B_{12} → Megaloblastic anemia.
4. Treatment of complications : as HF (*and mention* ☺)

Classification of Anemias

➲ Classification of anemias by Pathophysiology :

I. **Decreased production :**

- ↓↓ **Hb Synthesis :** Iron Deficiency anemia , Thalassemia , Anemia of chronic disease.
- ↓↓ **DNA Synthesis :** Megaloblastic anemia.
- ↓↓ **Stem Cell :** Aplastic anemia.

II. **Increased destruction :** Hemolytic anemia.

III. **Increased RBCs loss :** Acute-post-hemorrhagic anemia.

➲ Classification of anemias by cell size :

I. **Microcytic hypochromic :**

- ➲ Iorn deficiency anemia : defect in haem synthesis.
- ➲ Thalassemia : defect in globin synthesis.
- ➲ Anemia of chronic disease : defect in haem synthesis.
- ➲ Sideroblastic anemia : defect in haem synthesis.

II.**Normocytic normochromic :**

- ➲ Hemolytic anemia.
- ➲ Aplastic anemia.
- ➲ Acute-post-hemorrhagic anemia.
- ➲ Anemia of chronic disease.

III. **Macrocytic :**

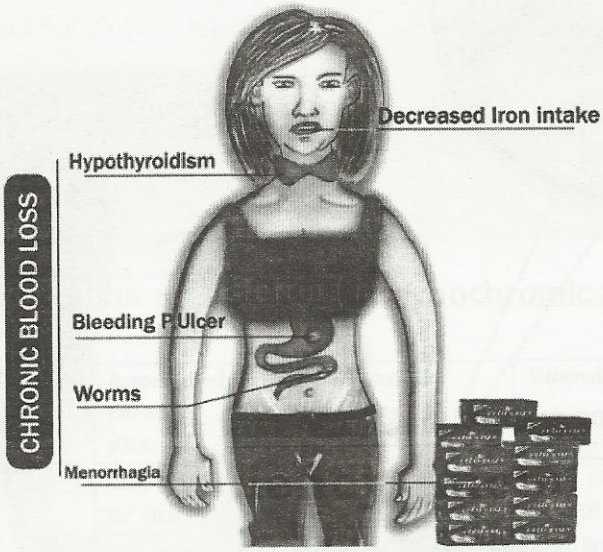
- ➲ Vitamin B_{12} deficiency.
- ➲ Folic acid deficiency.
- ➲ Myelodysplasia.
- ➲ Myxedema.
- ➲ Alcohol.
- ➲ Chronic liver diseases.

Iron Deficiency Anemia

{the most common type}

Etiology:

1. ***Chronic blood loss*** { the most common cause } e.g.
   - Menorrhagia.
   - Ancylostoma infection.
   - Esophageal varices , peptic ulcer.
2. ↓ Iron intake.
3. ↓ absorption of Iron :
   - Malabsorption syndrome.
   - Achlorhydria (↓ HCL) : notice that HCL is responsible for transformation of ferric form into ferrous to be absorbed.
4. ↑ Demand for Iron e.g. pregnancy , puberty.



Compensatory mechanisms : Iron deficiency leads to :

a. Increase absorption from the intestine.

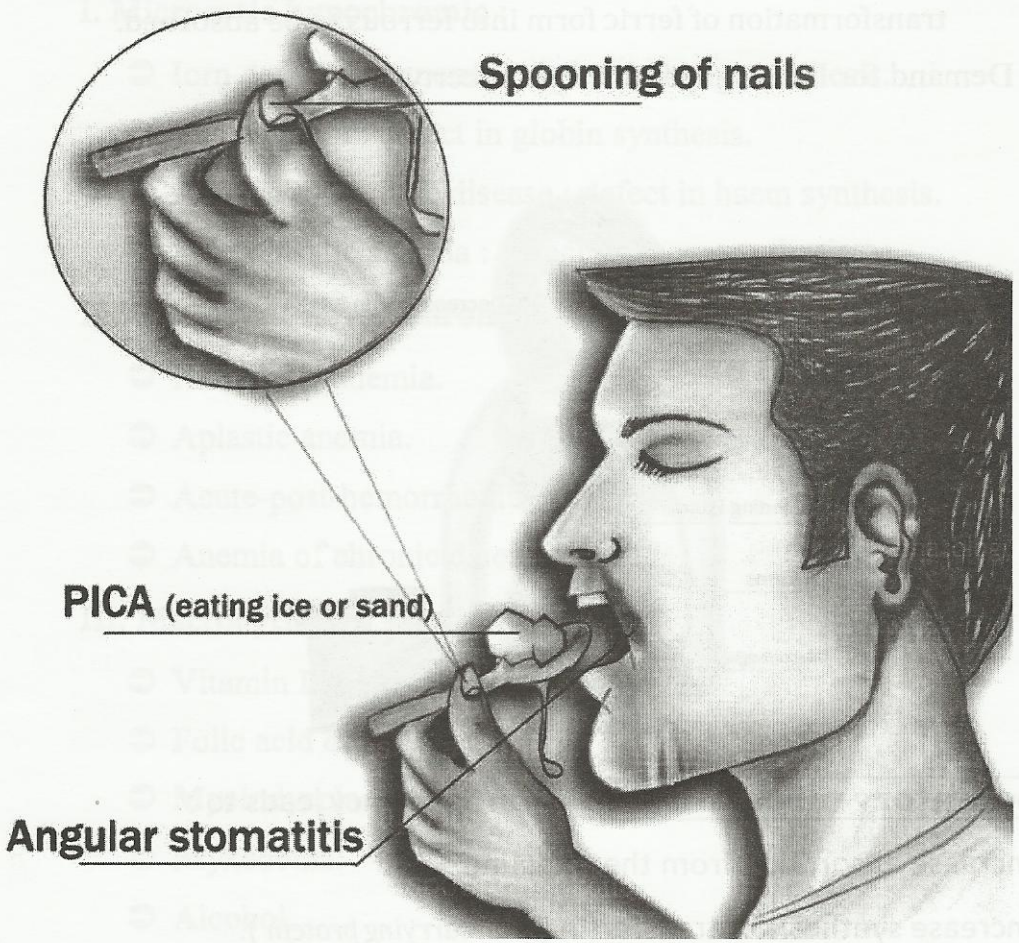
b. Increase synthesis of transferrin (*iron carrying protein*).

c. Decrease transferrin saturation (from 33% to 10%).

Clinical picture: as scheme plus

General manifestations of anemia *plus*

1. Pica ⇨ Perverted appetite.
2. Nails ⇨ Brittle and spooning (koilonychias)
3. Angular stomatitis & glossitis.
4. C/P of the cause :
   - Ancylostoma : GIT manifestations e.g. abdominal pain ....
   - Plummer - Vinson syndrome : Iron deficiency anemia with dysphagia.



Investigations : as Scheme

I. ***CBC :*** ↓↓ RBCs , Hb. ☺

↓↓ MCV, MCH , MCHC. (MCV < 80 fL , MCH < 27 pg).

II. ***Color Index :*** < 1

III. ***Bone Marrow Examinations :***

- Erythroid hyperplasia.
- Not essential for the diagnosis of iron deficiency.

IV. Iron Profile :

- ↓ serum iron and serum ferritin & transferrin saturation.
- ↑ Total Iron Binding Capacity (TIBC).

V. For the cause :

- Stool analysis for Ancylostoma : ova.
- Endoscope may be needed to detect the site of chronic blood loss e.g. peptic ulcer.

Differential diagnosis : Microcytic hypochromic anemia :

	Iron deficiency	Anemia of chronic disease	Thalassaemia trait (α or β)	Sideroblastic anemia
MCV	Reduced	Low normal or normal	Very low for degree of anemia	Low in inherited type but often raised in acquired type
Serum iron	Reduced	Reduced	Normal	Raised
Serum TIBC	Raised	Reduced	Normal	Normal
Serum ferritin	Reduced	Normal or raised	Normal	Raised
Iron in marrow	Absent	Present	Present	Present
Iron in erythroblasts	Absent	Absent or reduced	Present	Ring forms *Details : see below*

Treatment : as scheme plus

- Treatment of the cause e.g. ; Ancylostoma , peptic ulcer, menstruation …
- **Iron therapy :**

The response to iron therapy can be monitored using the reticulocyte count and Hb level (*Hb should rise by 1 gm% per week*)

1. **oral** : tab/8h
   - Ferrous sulphate 200 mg tab
   - Ferrous gluconate 300 mg tab
   - Vit C can be given to improve the absorption.
   - S/E : nausea , vomiting , abdominal pain , dark stool.
2. **parental** :
   - Indication :
     - Oral iron intolerance.
     - Malabsorption syndrome.
     - GI disorders that may be aggravated by oral iron e.g. peptic ulcer.
     - Rapid iron loss.
   - Preparation :
     - Iron-Dextran : 100 mg/d IM or IV
     - Iron-Sorbitol : 50 mg/d IM

Sideroblastic anemia

- Refractory anemia due to ineffective haem synthesis (*failure to incorporate iron into hemoglobin molecule*).
- There is accumulation of iron in the mitochondria of erythroblasts forming a ring of iron granules around the nucleus (*ring sideroblasts*)
- Causes :
  - Inherited : X-linked disease.
  - Acquired :
    - Primary : one of the myelodysplastic disorders (*see later*)
    - Secondary : **A**lcohol , Lead **p**oisoning , **C**ancer , **D**rugs e.g. INH.

Aplastic Anemia

Definition: Anemia due to Bone Marrow failure.

Etiology:

- *Primary:* Idiopathic : probably autoimmune { *the most common cause* }
- *Secondary:*

Replaced bone marrow : 3 M

- Malignancy : Leukemia , Lymphoma
- Myelofbrosis.
- Myelosclerosis.

Depressed bone marrow : 4 I

1) **I**rradiation.
2) **I**nfection : Hepatitis , EBV
3) **I**mmune : SLE
4) **I**atrogenic : any anti ... ☺
   - **Anti** biotics : Chloramphenicol
   - **Anti** neoplastic : Azathioprine
   - **Anti** epileptic : Phenytoin.
   - **Anti** DM : Chlorpropamide.
   - **Anti** thyroid : Carbimazole

Clinical picture:

- Anemia.
- Recurrent infections.
- Bleeding.

Investigations:

I. **CBC** :

- The hallmark of aplastic anemia is **pancytopenia**. However, early in the evolution of aplastic anemia, only one or two cell lines may be reduced.
- MCV , MCH , MCHC : normal.
- Decreased reticulocytes.

II. **Color index** : normal (1)

III. **Bone marrow examination** : Hypocellular , devoid of hematopoietic cells.

Treatment:

supportive ttt plus ***A , B , C***

- **Supportive treatment :** red cell transfusion for anemia , antibiotics for infections , platelet transfusion for bleeding.
- **Androgen.** (*B.M. stimulant*)
- **BM transplant :** in severe cases , particularly in children.
- **Cause treatment.**

DD of Pancytopenia

- Aplastic anemia (*and its causes*)
- Megaloplastic anemia.
- Hypersplenism (e.g. *portal HTN*)
- Myelofibrosis.
- Myelosclerosis.
- Subleukemic leukemia.
- PNH.
- SLE.

Megaloblastic anemia

Definition :

It's a hematological disorder characterized by Pancytopenia with 4 criteria: ♫ ♫

1. *Megaloplastic hyperplasia of the bone marrow.*
2. *Evidence of Macrocytosis .*
3. *Good response to vit. B12 & folic acid.*
4. *Neurological & G.I.T manifestations.*

Pathophysiology: 4

1. ***Arrest of the division*** : as vit. B12 & folic acid are essential for DNA synthesis. This will result in big cells (megaloblasts).
2. ***Ineffective erythropoesis*** : most of megaloblasts undego intra mdullary hemolysis.
3. ***Evidence of macrocytes*** : some megaloblasts can escape the bone marrow and appear in the blood as macrocytes.
4. ***Rapid hemolysis*** : macrocytes are rapidly sequestrated by the spleen.

Etiology:

I. Vitamin B_{12} deficiency : 4

1. Diminished intake of vitamin B12 which is present in animal products.
2. Decreased absorption :
   - **Pernicious anemia** (*The most common cause*)
   - Gasterectomy , chronic gastritis.
   - Malabsorption syndrome.
   - Ileal resection.
3. Chronic liver diseases : Body stores are Sufficient for 3yrs.
4. Transcobalamin II deficiency (rare)

Pernicious anemia

- I think you know that intrinsic factor is necessary for absorption of vitamin B12 ….. ok
- Here in pernicious anemia , there is a deficiency in production of intrinsic factor ….. why ?
- Most probably autoimmune disease in which there are auto antibodies against parietal cells (*anti parietal cell antibodies*)
- It is rare before 35 years , may be associated with prematurely grey hair & other autoimmune diseases e.g. Myxedema , vitiligo.

II. Folic acid deficiency :

1. **Decreased intake** : lack of vegetables & fruits , alcoholism.
2. Decreased absorption : malabsorption syndrome.
3. Increased requirement : Pregnancy , malignancy.
4. Drugs : Methotrexate , phenytoin. ***MCQ***

Clinical picture:

➲ Anemia : see scheme

➲ Neurological manifestations (3 p)

Vit B12 is an important co factor in the formation of myelin sheath.

1. Peripheral neuropathy.
2. Pyramidal tract lesion.
3. Posterior column → loss of deep sensations.

➲ gastrointestinal manifestations (3 Atrophy)

1. Atrophic glossitis.
2. Atrophic gastritis.
3. Atrophy in the intestine.

No Neurological manifestations in isolated folic acid deficiency

Investigations: As scheme plus

I. CBC :

- **Pancytopenia** : RBCs , Hb , WBCs & platelets : ↓↓
- MCV, MCH , MCHC : ↑ ***except*** MCHC is normal.
- Anisocytosis (*unequal size*) , Poikilocytosis (*abnormal shapes*)
- **Color index** : > 1

II. Bone marrow examinations : Megaloplastic hyperplasia ☺

III. Measurement of serum B_{12} & folic acid :

- serum B_{12} : < 100 pg/ mL (N : > 200 pg/ ml)
- serum folate : < 4 ng/ ml (N : 6 - 20 ng/ ml)

IV. Schilling test :

- Giving the patient vit. B_{12} (100 ug IV) to saturate body stores.
- Giving patient radioactive B_{12} (1ug) orally.
- Collect patient urine /24 h and measure radioactive B12
- If vitamin B_{12} is absorbed , it will appear in urine.

- Low excretion → Malabsorption.
- Normal after intrinsic factor orally→ Pernicious anemia.
- Normal after antibiotic → Bacterial overgrowth
- Normal after pancreatic enzymes → Pancreatic insufficiency.

V. Therapeutic test :

Giving small dose of vitamin B_{12} or folic acid → Reticulocytosis.

VI. Serological test :

Anti parietal cell antibodies & anti intrinsic factor antibodies may be present in pernicious anemia.

VII. FIGLU Test : +ve in folic acid deficiency.

Oral loading with histidine is accompanied by high urinary excretion of Formin Ino GLUtamic acid , an intermediate metabolite in the conversion of L-histidine to L-glutamic acid. (*+ve FIGLU test*).

Differential diagnosis :

Other causes of **mac**rocytic anemias :

- **M**yelodysplasia
- **M**yxedema.
- **A**lcohol.
- **C**hronic liver diseases.

Treatment: As scheme plus replacement therapy

1. ***Vitamin B_{12} deficiency :***

   Vitamin B_{12} (*Hydroxycobalamine*) :

   - Intramuscular injections of 1000 ug of vitamin B_{12} : usually given daily for the first week, weekly for the first month, and then monthly for life.
   - It is a lifelong disorder, and if patients discontinue their monthly therapy the vitamin deficiency will recur.

2. ***Folic acid deficiency :***

   - Folic acid : 5 mg/day orally
   - Vitamin B_{12} is essential for the transformation of folic acid into the active form folinic acid , So large doses of folic acid may aggravate the manifestations of vitamin B_{12} deficiency especially neurological manifestations.

Try to learn something about everything and everything about something.

Thomas Henry Huxley

Hemolytic anemias

Definition:

Anemias due to reduction of life span of RBCs (*increased rate of RBCs destruction*). N : 120 days

Etiology :

Corpuscular:

➲Membrane defect	Spherocytosis PNH ? Elliptocytosis.
➲Hb defect	Sickle cell anemia Thalassemia
➲Enzyme defect	G6PD Pyruvate kinase deficiency.

Extra-corpuscular:

1- Immune :
   - **Iso-immune :** Antibodies cause destruction of RBCs after transfer to another person e.g. ABO , Rh incompatibility.
   - **Auto-immune :** Antibodies cause destruction of RBCs of the same person e.g. warm & cold type (see later)
2- Infection : Malaria.
3- Toxic : Amphotericin B , Lead , Copper , snake venom , sulpha.
4- Trauma : Artificial valve , March hemoglobinuria , Micro-angiopathic hemolytic anemia e.g. vasculitis , DIC.
5- Hypersplenism.

Pathophysiology :

1- Anemia occurs if life span < 15 days : As bone marrow has ability to ↑ it's activity up to 8 times (*compensated hemolytic state*).

2- Hemolytic jaundice ⇨ ↑ unconjugated bilirubin.

3- Intravascular hemolysis : in the circulation ⇨ Hemoglobinuria ⇨ tubular damage and dark urine.

4- Extravascular hemolysis : in the reticulo-endthelial system (RES) ⇨ HepatoSplenomegaly.

Clinical picture:

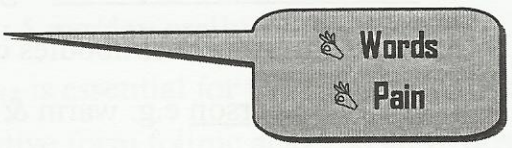
General manifestations of anemia (see before) ***Plus*** : 4

1- Manifestations of hemolytic jaundice (see GIT…wait ..see here ☺)
   - Jaundice: mild (lemon yellow)
   - Urine: Normal , may be dark due to hemglobinuria.
   - Stool: dark

2- Intravascular hemolysis ⇨ Hemoglobinuria.
   - Tubular damage.
   - Dark urine.

3- Extravascular hemolysis (in the reticulo-endthelial system , RES) ⇨ HepatoSplenomegaly.

4- Hemolytic crisis :



   1- Fever.
   2- Rigor.
   3- Deepening of jaundice.
   4- Bone ache → due to hyperactivation of the bone marrow.
   5- Kidney → Loin pain.
   6- Abdominal pain.

Different types of crisis

- ***Megaloblastic crisis*** : due to development of folic acid deficiency.
- ***Aplastic crisis*** : viral infection → inhibition of BM → aggravation of anemia without deepening of jaundice.
- ***Vaso-occlusive crisis*** (in sickle cell anemia → Occlusion Of Small Blood Vessels)

Don't forget features of certain types of hemolytic anemias (see below)

Investigations :

1- **CBC**

- ↓↓ RBCs , Hb ☺
- Normal WBCs & platelets.
- Normal MCV , MCH & MCHC.
- **↑↑ Reticulocytic count** Except in Aplastic crisis.

Reticulocytic count is the single test to detect hemolytic anemia.

2- **Color index** = 1

3- **BM examination** :

- **Hypercellular to compensate for RBCs destruction.**
- Normoblasts.
- Megaloplastic : in secondary folic acid deficiency

4- **Investigations for hemolytic jaundice:**

- ***In serum***: ↖ !unconjugated bilirubin.
  (Bilirubin never > 5mg% as long as liver is normal)
- ***In stool*** : ↖ !sterocobilinogen. (dark stool)
- ***In urine*** :
  - Unconjugated bilirubin is *water insoluble* therefore NOT found in urine. (normal colored urine)
  - ↖ !urobilinogen .

5- ↓↓ **RBCs life span :** measured by isotopic methods.

6- **Investigations for intravascular hemolysis** :

- Hemoglobinuria.
- Diminished hemopexin & haptoglobin in plasma. (*normal plasma proteins that bind and clear hemoglobin released into plasma*)

7- **Investigations for certain types of hemolytic anemias** : *see below*

Coomb's test * :

- A test for detection of antibodies against RBCs
- Positive in immune hemolytic anemia.
- Either :
  - Direct : detects antibodies on surface of RBCs.
  - Indirect : detects antibodies in plasma.

* The Coombs reagent is a rabbit IgM antibody raised against human IgG. The direct Coombs test is performed by mixing the patient's red blood cells with the Coombs reagent and looking for agglutination, which indicates the presence of antibody on the red blood cell surface.

Treatment :

1- Fresh blood transfusion.

2- Splenectomy in some cases.

3- Treatment of the cause : if possible.

I have not failed. I've just found 10,000 ways that won't work.

Thomas Edison

Hereditary Spherocytosis

Definition :

Hereditary spherocytosis is a disorder of the RBCs membrane in which there is a deficiency in *spectrin* protein in RBCs membrane . so the membrane becomes :

i. **Rigid :** so the RBCs are trapped in the small capillaries & spleen & rapidly destroyed.

(Normally, the red blood cell is a biconcave disk with a diameter of 7 mcm. The red blood cells must be deformable to pass through capillaries 3 mcm in diameter)

ii. **Highly permeable to Na & water :** causing the RBCs to take the shape of sphere & early destruction occurs.

Clinical picture :

- Features of hemolytic anemia (see before)
- +ve family history is usually +ve.
- The onset is usually during childhood.

Investigations : The same as hemolytic anemias *plus*

1. **Osmotic fragility :** is increased , hemolysis occurs at dilution of 0.7% *(normally RBCs hemolysis occurs at dilution less than 0.4 %).*
2. Blood film : spherocytes.
3. **Increased MCHC** : Hereditary spherocytosis is the only important disorder associated with microcytosis and an increased MCHC.

Treatment :

1. Blood transfusion.
2. Splenectomy : Best avoided in patients < 10 years old due to risk of fatal infection postsplenectomy. Remember pre-splenectomy vaccines and post-splenectomy antibiotics.
3. Folic acid 1mg/d.

Paroxysmal Nocturnal Hemoglobinurea (PNH)

Definition :

Blood cells membranes are more sensitive to **complement** system .

Clinical picture : *Triad of*

1- *Chronic hemolytic anemia : particularly overnight*

at night → hypoventilation → ↑ CO_2 → acidosis → activation of C_3

2- *Pancytopenia :* due to associated BM hypoplasia.

3- *Thrombosis* (e.g. Budd–Chiari syndrome).

Complications :

- May progress to more severe aplastic anemia.
- Transforms to acute leukemia in 5%.
- Serious thrombosis in up to 20%.

Investigations :

- Ham test : +ve (rapid hemolysis occurs if the serum is acidified)
- Flow cytometric assays may confirm the diagnosis (absence of CD59)

Treatment : General supportive measures *plus* :

1- Steroid.

2- Oral anticoagulants for thrombosis.

3- BM transplant.

G6PD deficiency

(Glucose 6 Phosphate Dehydrogenase deficiency)

- G6PD enzyme is essential for production of reduced glutathione *(through Hexose monophosphate shunt)* which protects RBCs from oxidizing agents.
- In the absence of reduced glutathione, hemoglobin may become oxidized.
- It is X-linked disease affects mainly ♂. ☹

Clinical picture :

i. When patient is subjected to oxidizing stress → acute intravascular hemolysis occurs.

ii. Oxidizing agents :

- Drugs :
  - Anti-malarial : Primaquine , Chloroquine.
  - Anti biotics : Sulphonamides (cotrimoxazole) , ciprofloxacin.
  - Aspirin.
- Diet : Fava bean (Favism)
- Infections.

iii. Types :

- Type A : (*Negro type*) :

  Enzyme defect in old RBCs only , so the hemolysis is not severe.

- Type B : (*Mediterranean type*)

  Enzyme defect in all RBCs (old , recent) , so the manifestations are severe.

- Favism : *In Mediterranean populations*
  - Hours/days after ingestion *(or even smelling)* of fava beans.
  - Beans contain oxidants e.g. vicine and convicine.
  - It may be *fatal*.

Investigations :

- Investigations for hemolysis. (*see before*)
- Assay of the **activity of G6PD enzyme.**
- Blood film : *Heinz bodies*.

Treatment :

- Avoid oxidizing agents.
- Blood transfusion in severe attacks.

Autoimmune hemolytic anemia

Definition : an acquired anemia caused by auto-antibodies.

Types :

I. Warm type :

Extravascular RBC destruction by RES mediated by warm-reacting antibody.

Etiology :

- Most cases are idiopathic. (75%)
- Secondary : Lymphoma , leukemia , SLE , Drugs : α methyl dopa.

Clinical picture :

- Features of hemolytic anemia.
- DIC

Investigations :

- Investigations for diagnosis of hemolysis : *see before*
- **Positive Coomb's test** : Detects antibodies on RBCs (IgG)
- Blood films : spherocytes. *(when IgG attacks RBCs they become spherocytes)*
- Immune thrombocytopenia may be associated (*Evans's syndrome*)

Treatment :

- Prednisone : 1 mg/kg/d orally
- Immunosuppressive drugs e.g. azathioprine.
- Splenectomy .

II. Cold type : (*Cold haemagglutinin disease*)

Caused by RBC antibodies that reacts most strongly at temperatures < 37°C.

Etiology :

- Idiopathic.
- Infectious Mononucleosis , Mycoplasma pneumonia , Paroxysmal cold haemoglobinuria.

Clinical picture :

- Hemolytic anemia on exposure to cold.
- Raynaud's phenomenon.

Investigations :

- General investigations for hemolysis.
- Positive Coomb's test.

Treatment :

- Avoid exposure to cold.
- Cyclophosphamide.
- Azathioprine.

	Warm type	Cold type
Temperature at which antibody attaches best to red cells	37°C	Lower than 37°C
Type of antibody	IgG	IgM
Direct Coombs' test	Strongly positive	Positive
Causes :	o Idiopathic o Lymphoma . o Leukemia. o SLE. o Drugs(methyl dopa)	o Idiopathic o Infectious Mononucleosis . o Mycoplasma pneumonia. o Paroxysmal cold haemoglobinuria.

Hemoglobinopathies

Hemoglobin is composed of :

- Haem : Iron - protoporphyrin complex.
- Globin : protein consisting of 4 polypeptide chains.

Hemoglobin	Globin chains	Amount
Fetus :		
Hb F	$\alpha_2\gamma_2$	85%
Hb A	$\alpha_2\beta_2$	5 - 10%
Adult :		
Hb A	$\alpha_2\beta_2$	97 %
Hb A_2	$\alpha_2\delta_2$	2.5 %
Hb F	$\alpha_2\gamma_2$	0.5 %

Sickle cell anemia

Definition :

- Hereditary disorder in which there is production of abnormal Hb (HbS)
- In Hb S : valine replaces glutamic acid at position 6 *on the β-globin chain.*
- **It is of 2 types** :

1) Homozygous (*sickle cell anemia*) : HbSS

   Leading to manifested anemia , sickling (*elongation*) may occur with mild hypoxia.

2) Heterozygous (*sickle cell trait*) : HbAS

   It is asymptomatic , sickling may occur with severe hypoxia.

Clinical picture :

- General manifestations of hemolytic anemia **without splenomegaly**
- Vaso-occlusive crisis :

  abnormal sickling (*elongation*) of RBCs ⇨ vaso occlusion ⇨ Tissue infarction resulting in pain and/or tissue damage.

  - Brain : strokes.
  - Eye : retinal detachment.
  - Heart : myocardial infarction.

- Spleen : infarction ⇨ autosplenectomy (No splenomegaly)
- Kidney : infarction (hematuria & chronic renal failure)
- Abdomen : Mesenteric blood vessels occlusion ⇨ acute abdomen.
- Bone : pain.
- Penis : priapism.
- Leg ulcers.

➲ Infections : pneumococci and salmonella.

Investigations :

- Investigations for diagnosis of hemolytic anemia.
- Hb electrophoresis → HbS is high (diagnostic)
- Blood film→ sickle cells especially after inducing hypoxia by addition of Na metebisulphite.

Treatment :

1) Blood transfusion.
2) Symptomatic treatment :
   - Analgesics.
   - O2 therapy.
   - IV fluids
   - Exchange blood transfusion (if stroke or visceral damage) : Aim to ↓ HbS to < 30%.
   - Pneumococcal vaccination.
3) New lines of treatment :
   - Hydroxyurea : elevates HbF *(HbF reduces HbS and hence sickling)*
   - BMT.
   - Gene therapy.

Thalassaemia

Definition :

- Hereditary disorders characterized by reduction in the synthesis of globin chains (α or ß).
- Reduced globin chain synthesis causes reduced hemoglobin synthesis and eventually produces a hypochromic microcytic anemia because of defective hemoglobinization of red blood cells.

Types :

1- Alpha thalassaemia :

- There is decreased production of α chains.
- There are 4 α gene. The disease is caused by gene deletion as follow :

α-Globin Genes	Syndrome	Comment
1 gene deletion	Silent carrier	Asymptomatic
2 gene deletion	α Thalassemia minor (trait)	○ Mild Hypochromic microcytic anemia. ○ Usually diagnosed by exclusion (other causes of microcytic anemia are excluded e.g. iron deficiency). ○ No splenomegaly. ○ Requires no therapy.
3 gene deletion	**Hemoglobin H disease** Hb H ($ß_4$) is 30 - 40%	○ Hypochromic microcytic anemia. ○ Splenomegaly. ○ Treatment : blood transfusion , folic acid & Splenectomy in some cases.
4 gene deletion	**α thalassaemia major** Hb H & Hb Bart ($γ_4$) : > 80%	There is a major failure of α chain manufacture, death in utero results (*Hydrops fetalis*).

2- Beta thalassaemia :

- There is decreased production of ß chains which are replaced by gamma (γ) or delta (δ) chains leading to production of Hb F ($\alpha_2\gamma_2$) & HbA_2 ($\alpha_2\delta_2$).

N : 97% of Hb is Hb A (α_2 $ß_2$)

- **There are 3 types :**

1) **Thalassaemia major :** (Cooley's anemia)

- Hb A is markedly reduced &Hb F is markedly increased (90%)
- Clinical manifestations :
  - Starts after the age of 6 months (*when hemoglobin synthesis switches from hemoglobin F to hemoglobin A*) .
  - Severe anemia requiring lifelong blood transfusion.
  - Hepatosplenomegaly , hypersplenism.
  - Growth retardation : due to chronic anemia.
  - Bony deformities :
    I. Flat bones , pathologic fractures.
    II. Facial appearance :
      - ✓ Protrusion of frontal & parietal bones.
      - ✓ Prominence of malar eminences & prognathism.
      - ✓ Depressed nasal bridges.
  - Hemochromatosis (Cirrhosis , HF , DM ...) : see GIT p16

    It is due to transfusional iron overload. This problem develop because of the body's inability to excrete the iron from transfused red cells.

2) **Thalassaemia minor :** (*Thalassaemia trait*)
   - Hb A is slightly reduced with increase in both Hb F (5 - 10%) & Hb A_2 (5 - 10%). It presents in adults by mild anemia & splenomegaly.
   - Usually requires no treatment.

3) **Thalassaemia intermedia :** variable Hb A .
   - NOT requiring regular blood transfusion.
   - more severe than thalassaemia trait but milder than thalassaemia major.

Causes of death :

1. Congestive heart failure.
2. Recurrent chest infections.
3. Multiple organ failure (MOF)

Investigations :

1) Peripheral blood examination :
   - RBCs & Hb : ↓ ☺
   - Microcytic hypochromic anemia. (↓ MCV , MCH , MCHC)
   - Target cells , Aniso- & poikilocytosis.
2) **Hb electrophoresis** : diagnostic
   - ☞ Thalassemia major : Hb A is markedly reduced & Hb F is markedly increased (90%).
   - ☞ Thalassemia minor : ↑ Hb A_2
3) X-ray :
   - Skull : **Hair on end appearance**.
   - Long bones : thin cortex , wide medulla.
4) Serum **iron** & ferritin : **Increased**.

Treatment :

1. **Blood transfusion :**
   - o Thalassaemia major : requiring lifelong blood transfusion.
   - o Thalassaemia intermedia : NOT requiring regular blood transfusion.
   - o Thalassaemia minor : Usually requires no treatment.

   Aim of blood transfusion : to keep Hb concentration
   - ✓ > 6 gm/dl : simple transfusion.
   - ✓ > 10 gm/dl : hyper-transfusion.
   - ✓ > 12 gm/dl : super-transfusion.
2. Avoid diet rich in iron.
3. Iron chelating agent :
   - Desferrioxamine (*desferal*) : IM , SC.
   - Deferasirox : oral.
4. Folic acid : 1mg/d oral.
5. Antibiotics : for recurrent infections.
6. **Splenectomy** : may be indicated especially in a case of hypersplenism.
7. **BM transplant** : The most efficient.

A doctor must work eighteen hours a day and seven days a week. If you cannot console yourself to this, get out of the profession.

Martin H. Fischer

Anemia of chronic disease

Definition :

It is a form of anemia seen in chronic illness e.g. chronic infection, chronic inflammation, liver disease, renal failure, or malignancy.

Incidence : *the 2nd most common type next to iron deficiency anemia*

Pathophysiology : *(failure of iron utilization)*

- ↓ Life span of RBCs
- Failure of B.M to compensate is due to sequestration of iron in RES
- ↓ Erythropoietin is rarely an important factor ***except*** in renal failure.

Clinical picture :

- Clinical picture of the cause
- Clinical picture of anemia (*see scheme and you **may** remember*)

Investigations :

- Serum iron : ↓↓
- Transferrin saturation may be extremely low.
- TIBC : ↓↓
- **Serum ferritin** : normal or increased (*In contrast to iron deficiency*)
- For the cause : KFTs, LFTs, Tumor markers.

Treatment :

- In most cases no treatment is necessary as it is usually mild anemia
- Treatment of the cause.
- Erythropoietin.

	Iron deficiency	Anemia of chronic disease
MCV	Reduced	Low normal or normal
Serum iron	Reduced	Reduced
Serum TIBC	Raised	Reduced
Serum ferritin	Reduced	Normal or raised
Iron in marrow	Absent	Present

Anemia of Chronic Renal Insufficiency

Etiology :

This condition is attributed primarily to decreased erythropoietin production and may occur as the creatinine clearance declines below approximately 50 mL/min.

Diagnosis :

- CBC : Normocytic anemia.
- Clinical picture & investigations of chronic renal failure.

Treatment :

- **Erythropoietin.**

  Adverse reactions :

  - Hypertension , seizures may occur.
  - Suboptimal responses may occur with coexisting iron deficiency so, many patients benefit from IV iron supplementation.

Anemia in endocrine disease

PITUITARY :

- **Panhypopituitarism** : is associated with normochromic, normocytic anemia , associated leucopenia may also occur.

THYROID :

- **Hypothyroidism** : may produce a mild degree of anemia.
  - ✓ Menorrhagia occurs in hypothyroidism and can result in associated Fe deficiency.
  - ✓ B12 levels should be checked because of the association with other autoimmune disorders (e.g. pernicious anemia).

ADRENAL :

- **Hypoadrenalism** : results in normochromic, normocytic anemia, the plasma volume is ↓ which masks the true degree of associated anemia. The abnormalities are corrected by replacement mineralocorticoids.
- **Cushing's** : results in erythrocytosis with a typical net increase in Hb (by 1–2g/dL). Mechanism is unclear.

PARATHYROID :

- **Hyperparathyroidism** : may be associated with anemia from impairment of erythropoietin production, or in some cases from secondary marrow sclerosis.

DIABETES MELLITUS :

When poorly controlled may be associated with anemia; however, the majority of hematological abnormalities in diabetes mellitus result from secondary disease related complications e.g. renal failure.

Any other type of Anemia

(anemia of liver failure or pregnancy)

Scheme + use your mind ☺

DISORDERS OF WHITE CELLS

LEUCOCYTOSIS

Neutrophils (PMNs , Polymorphonuclear Neutrophils) : 50–70 %

This is by far the commonest cause of Leucocytosis.

Increased :

A. *Physiological :* Severe exercise, last months of pregnancy, newborn, steroids.

B. *Pathological :*

- Bacterial infection.
- Non-infective tissue damage : MI , pulmonary infarction , pancreatitis, burn .
- Metabolic disorder : DKA, uremia, acute gout
- Myeloproliferative disorders.

Decreased:

a mild decrease is referred to as **neutropenia**; a severe decrease is called **agranulocytosis**.

- **I**nfection : viral , Typhoid , Brucella.
- **I**mmunological : SLE , Felty's syndrome.
- **I**atrogenic : cytotoxic agents, phenothiazines, NSAIDs, anti-thyroid drugs.
- Aplastic anemia.
- Hypersplenism.
- Benign familial neutropenia : is a feature of rare families , is associated with mild neutropenia but no propensity to infection.

Basophils : 0–1%

Function : They combine with IgE causing release of histamine & other contents involved in acute hypersensitivity.

Increased:

- Myeloproliferative disorders e.g. CML , polycythemia vera.
- Hodgkin disease.
- Rarely : recovery from infection or hypothyroidism.

Decreased : Acute rheumatic fever, pregnancy , steroid therapy, thyrotoxicosis, stress.

Eosinophils : 1 – 5 %

Increased:

- **A**llergy : Bronchial Asthma, Eczema.
- **A**sthma.
- **A**ddison disease.
- **A**nkylostomiasis , Ascariasis.

Decreased : Steroids, Cushing syndrome , Acute stressful conditions.

Lymphocytes : 20 – 45 %

Increased:

- Viral infection : measles, mumps, smallpox, influenza, hepatitis, infectious mononucleosis).
- Bacterial infection : TB , brucella , typhoid.
- acute and chronic lymphocytic leukemia
- Lymphocytosis is normal in infancy.

Decreased: Normal in 22% of population.

- **S**tress.
- **S**teroids.
- **S**uppression of BM after chemotherapy.
- **S**LE.
- **S**ome viral infections e.g. HIV ☺

Atypical Lymphocytosis :

- Infectious mononucleosis , CMV , toxoplasmosis.
- Viral hepatitis.
- Leukemia & lymphoma.

Monocytes : 3 – 7 %

They originate in the BM then circulate in the blood ⇨ to the tissue (converted into tissue **macrophages**).

Increased :

- Infection : TB, SBE, brucellosis, typhoid , infectious mononucleosis , malaria.
- leukemia, Hodgkin disease.
- Inflammatory bowel disease : ulcerative colitis.

Decreased : Lymphocytic leukemia, aplastic anemia, steroid use.

LEUKEMIA

Definition :

Malignant proliferation of immature WBCs primarily in bone marrow & then they circulate in peripheral blood & infiltrate other tissues.

Classification of leukemia :

I. Acute leukemia
- Acute Lymphoblastic leukemia (*ALL*)
- Acute Myeloblastic leukemia (*AML* , *ANLL*)

II. Chronic leukemia
- Chronic myeloid leukemia (*CML*)
- Chronic Lymphocytic leukemia (*CLL*)

Etiology : *Unknown but genetic & environmental factors may play a role*:

I. Genetic factor :
- The incidence of leukaemia is increased in identical twins.
- High incidence in certain chromosomal disorders : Down's syndrome, Klinefelter's syndrome.
- Presence of chromosomal abnormalities in certain types of leukemia e.g. Philadelphia chromosome in CML.

II. Environmental :
- **Radiation** : Increased incidences in survivors of Hiroshima and Nagasaki and in patients treated with ionizing radiation.
- **Chemical and drugs** : benzene, chlorambucil.
- **Viruses :** Leukaemias are associated with human T cell lymphotropic virus (HTLV-I), which is found particularly in Japan and the Caribbean.

III.Pre - existing hematologic disorders : Myelodysplastic syndromes.

Acute Leukemia

Definition:

Malignant proliferation of immature WBCs " **blast cells**".

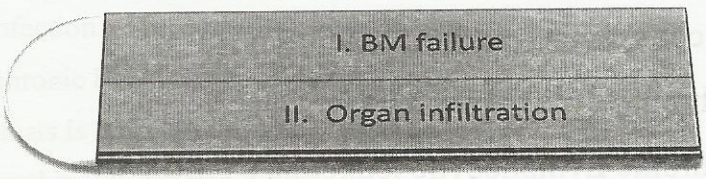
Classification :

I. **Acute lymphoblastic leukemia** (ALL) : common in children (*80% of the acute leukemias of childhood*). The peak incidence is between 3 and 7 years.

II. **Acute myeloblastic leukemia** (AML) : common in adults.

clinical picture :

2 problems



I. Bone Marrow failure :

Blast cells proliferate in an uncontrolled fashion and replace normal bone marrow elements.

- RBCs : Severe progressive anemia.
- Platelets : purpura, menorrhagia, epistaxis & bleeding gums, rectal, retina.
- WBCs : Fever & recurrent infections .
  - The most common pathogens are gram-negative bacteria (E coli, Klebsiella, Pseudomonas) or fungi (Candida, Aspergillus).
  - Common presentations include cellulitis, pneumonia, UTI and perirectal infections; death within a few hours may occur if treatment with appropriate antibiotics is delayed.

II. Organ Infiltration :

1. Bone marrow infiltration : bone pain , **tender sternum**.
2. Generalized lymphadenopathy especially in ALL (e.g. Cervical , *mediastinal* , porta hepatis LN)
3. ***Hepatosplenomegaly.***

4. Other organs affection :

- **Inf**iltration.
- **Inf**ection.
- **Inf**arction : due to leucostasis (*occlusion of the microcirculation leading to ischemia & hemorrhage*).

e.g. :

- ***Kidney :*** Acute renal failure especially during treatment, pyelonephritis.
- ***Skin :*** pruritis , nodules , **chloromas** (*soft tissue masses that may occur in AML*). MCQ
- ***CVS :*** cardiomyopathy.
- ***CNS :*** Paraplegia , meningitis , ↑ ICT.
- ***Lung :*** Hemoptysis , infections.
- ***Gum hypertrophy.***
- Testicular infiltration & penis priapism.

Investigations:

☑ *CBC* :

- WBCs : usually increased (up to 100,000/ cmm) , but WBCs may be low
- RBCs : ↓↓ normocytic normochromic anemia.
- Platelets ↓↓
- **Blast Cells** : +++ *(lymphoblasts or myeloblasts)*
- Cytochemical stains, immunological markers & cytogenetic analysis are necessary to differentiate AML from ALL.

Subleukemic leukemia :subnormal WBCs with presence of blasts.
Aleukemic leukemia: no blast cells.

☑ *BM examination* :

- More than 20% blasts are required to make a diagnosis of acute leukemia.

☑ *Others* :

- Uric acid , LDH : ↑

- Serum electrolytes may be affected due to diarrhea , vomiting or chemotherapy.
- CT brain , CSF examination , renal function tests.

How to differentiate between ALL & AML ?

- Morphology : Myeloblasts look similar to lymphoblasts. Presence of Auer rods in the cytoplasm of blasts are diagnostic of AML. **MCQ**
- Cytochemical stains : Sudan black stain is +ve in AML , -ve in ALL.
- Enzymes : ↑ Deaminase in ALL , Muramidase enzyme in AML.
- Immunological markers .

French-American-British (FAB) Classification of AML : Morphological background

- M0: Undifferentiated leukemia.
- M1: Myeloblastic leukemia without maturation.
- M2: Myeloblastic leukemia with maturation.
- M3: Promyelocytic leukemia : **often associated with DIC** *MCQ*
- M4: Myelomonocytic leukemia.
- M5: Monocytic leukemia.
- M6: Erythroleukemia : red blood cell precursors & myeloid blasts.
- M7: Megakaryoblastic leukemia : extremely variable morphology, very bad prognosis.

French-American-British (FAB) Classification of ALL :

- L1 : Cells are small & homogenous (child variant)
- L2 : Cells are large & heterogeneous (adult variant)
- L3 : Large Burkitt - like cells (aggressive type , associated with Burkitt's lymphoma)

Differential diagnosis:

1. Causes of fever with sore throat : Rheumatic fever , Infectious mononucleosis.
2. Bone marrow failure (Aplastic anemia) .
3. Causes of lymphadenopathy.

Treatment:

I. General supportive treatment :

- RBC and platelet transfusion will continue through treatment.
- Antibiotics for infection.
- Allopurinol to prevent hyperuricemia.

II. Chemotherapy :

Acute lymphoblastic leukemia : 4 steps :

1. *Induction of remission* VAP

Aim : is to achieve a complete remission (*no evidence of leukaemia in the blood, a normal blood count & < 5% blasts in the bone marrow*).

- ☑ Vincristine : 1.8 mg/m²/week IV for about 4 weeks.
- ☑ Adriamycin : 40 mg/m²/week IV for about 4 weeks.
- ☑ Prednisolone : 40 mg/m²/d oral for about 4 weeks.

Poor prognosis : MCQ

- Age < 2 or > 10 years. - WBCs > 50,000 . - CNS manifestations
- Platelets < 25000 - FAB classification : L3

2. *CNS prophylaxis :*

- ☑ Cranial irradiation.
- ☑ Intrathecal methotrexate.

3. *Consolidation* :

- Consolidation therapy is given after complete remission is achieved, to reduce the risk of relapse.
- It consists of either the same drugs as those used in induction therapy or other cytotoxics.

4. *Maintenance* : *for about 2- 3 years*

- ☑ Mercaptopurine (daily)
- ☑ Methotrexate. (weekly)
- ☑ Prednisolone (monthly)

Acute myeloplastic leukemia :

1. Induction of remission

- ☑ Cytosine arabinoside (*ara-c*) : 100 mg/m²/d for about I week.
- ☑ Adriamycin (Doxorubicin) : 45 mg/m² IV for 3 days.

2. CNS prophylaxis :

Is **NOT** used in the treatment of adult AML.

3. Consolidation :

It consists of either the same drugs as those used in induction therapy or other cytotoxics.

4. Maintenance therapy :

In the treatment of AML, there is controversy over the use of maintenance therapy. (*not thought to be of benefit in most patients with AML*). **Bone marrow transplantation is the treatment of choice**.

> **In general,** *the response to treatment and the prognosis are better in patients with ALL than in those with AML*

Prognosis :

- Without treatment : Acute leukemia is fatal within few months.
- Cure rate with chemotherapy :
  - ALL :
    - Children : 90%
    - Adults : 60%
  - AML : 30% (over 60s do worse)

Causes of death:

1. Recurrent infections
2. Cerebral or internal hemorrhage.
3. Multiple organ failure (**MOF**).

Chronic Myeloid Leukemia

Definition :

Chronic myeloid leukemia (CML) is a myeloproliferative disorder characterized by overproduction of myeloid cells.

Clinical picture:

CML is more common in middle & old age males ☹

- 30% asymptomatic at diagnosis; present after routine CBC.
- Fatigue & weight loss.

I. Organ Infiltration :

The same as in acute leukemia but begin with splenomegaly.

- **Splenomegaly (huge spleen) :**
  - Dragging pain in the left hypochondrium.
  - Stitching pain in the left hypochondrium due to splenic infarction.
  - The spleen is hugely enlarged , may be with multiple notches & splenic rub.
- Generalized lymphadenopathy (e.g. Cervical , *mediastinal* , porta hepatis LN) may occur.
- Bone marrow infiltration : bone pain , **tender sternum**.
- Other organs affection : rare in CML
  - **Infection.**
  - **Infiltration.**
  - **Infarction** : due to leucostasis (*occlusion of the microcirculation leading to ischemia & hemorrhage*).

e.g. :

- ***Kidney :*** Acute renal failure especially during treatment, pyelonephritis.
- ***Skin :*** pruritis , nodules.
- ***CVS :*** cardiomyopathy.
- ***CNS :*** Paraplegia , meningitis , ↑ ICT.
- ***Lung :*** Hemoptysis , infections.
- ***Gum hypertrophy.***
- Testicular infiltration & penis priapism.

II. Bone Marrow failure :

- RBCs : anemia.
- Platelets : purpura, menorrhagia, epistaxis & bleeding gums, rectal, retina.
- WBCs : Fever & recurrent infections .

III. Blastic crisis :

Patients may develop a transformation into acute myeloblastic leukemia.

Investigations :

☑ CBC

1. WBCs :
   - The total white cell count is increased (often > 100000/cmm)
   - It is mainly in the form of myelocytes & promyelocytes.
   - Myeloblasts is usually < 5% . Marked myeloblasts occur in blastic crisis.
2. RBCs : ↓ but not as those in acute leukemia.
3. Platelets: initial rise but drop with the progress of disease.

☑ B.M examination:

1. Hypercellular & full of myelocytes with few Myeloblasts.
2. Marked increase in Myeloblasts occurs in blastic crisis.

☑ The Philadelphia chromosome (Ph) :

- It is a translocation between chromosomes 9 and 22.
- It appears in all bone marrow derived cells except T cells. **MCQ**
- Positive in most cases (> 90%)
- Philadelphia +ve patients have a better prognosis than Philadelphia -ve patients.

☑ Others :

1. Uric acid & LDH : ↑
2. Neutrophil alkaline phosphatase (NAP) : ↓

Differential diagnosis :

1- **DD of huge splenomegaly :**

- Bilharziasis.
- Malaria.
- Chronic myeloid leukemia.
- Hairy cell leukemia.
- Thalassemia.
- Polycythemia.
- Myelofibrosis & Myelosclerosis.

2- **Leukemoid reaction :**

- Marked Leucocytosis (50,000/cmm) due to aggressive response of the bone marrow.
- Causes :
  - Infection (severe, chronic, e.g.TB).
  - Severe hemolysis.
  - Paramalignant syndrome.
- May be distinguished from chronic myeloid leukemia (CML) by measurement of the neutrophil alkaline phosphatase *(NAP)* : elevated or normal in leukemoid reactions, depressed in CML.

Treatment :

I. **General supportive treatment :** The same as acute leukemia

- RBC and platelet transfusion.
- Antibiotics for infection.
- Allopurinol to prevent hyperuricemia.
- Leukapheresis : for leukostasis.

II. Chemotherapy:

1. Busulfan (*Myeleran*) :
   - 4- 8 mg/d orally, The dose is reduced with reduction of TLC.
   - S/E : Aplastic anemia , vomiting , diarrhea , gonadal atrophy.
2. **Hydroxyurea** :
   - 1 - 6 gm/d orally , The dose is reduced with reduction of TLC.
   - Side effects: rash, mouth ulcers and diarrhea.

III. Radiotherapy : Irradiation of spleen in cases of huge spleen.

IV. Bone Marrow transplant : Option of choice in young & fit patient.

V. Treatment of plastic crisis : Similar to AML (*see above*)

Other drugs recently used in CML :

- Interferon : 3 million units SC , 3 times weekly
- **Imatinib** : tyrosine kinase inhibitor . dose : 400 mg/d orally.

Chronic Lymphocytic Leukemia

Definition :

- This is a malignant proliferation of small lymphocytes almost always (99%) B lymphocytes.
- Commonest leukemia in adults (*25–30% of all leukemia*).

Clinical picture:

- CLL is a disease of older patients : > 50 years.
- ♂ : ♀ ratio ~ 2 : 1 ☹
- Often asymptomatic , lymphocytosis on routine CBC.
- **Lymphadenopathy**: painless, often symmetrical.
- splenomegaly & hepatomegaly (50%)
- **BM failure** due to infiltration :
  - ✓ Anemia
  - ✓ Thrombocytopenia & bleeding tendency.
  - ✓ Recurrent infection due to acquired hypogammaglobulinemia especially Herpes zoster.
- Patients with advanced disease: weight loss, night sweats & malaise.

Staging of CLL : (Rai modified staging)

- stage 0 : Lymphocytosis only.
- stage I : Lymphocytosis plus lymphadenopathy.
- stage II : Lymphocytosis & organomegaly.
- stage III : Lymphocytosis & anemia.
- stage IV : Lymphocytosis & thrombocytopenia.

Investigations :

☑ CBC :

1. WBCs :
   - ✓ The hallmark of CLL is isolated lymphocytosis .

- ✓ The white blood count : ↑↑ and may be markedly elevated up to 1000000/cmm .
- ✓ Usually 80% of the circulating cells are lymphocytes.
- ✓ Lymphocytes appear small and mature.

2. RBCs and platelet count :
   - ✓ Usually normal at presentation.
   - ✓ Autoimmune hemolysis or autoimmune thrombocytopenia may occur in late stage.

☑ **BM examination :** > 30% lymphocytes.

☑ **Lymph node biopsy** :

Rarely required, appearances of lymphocytic lymphoma.

Treatment :

Many patient with CLL require no treatment , *living at peace with their lymphocytosis to die of an unrelated complaint.*

☑ ***supportive treatment :*** *as usual* (see CML)

☑ ***specific treatment:***

1. ***Chemotherapy*** : Chlorambucil (Leukeran) : 6 - 10 mg/d orally.
2. ***Radiotherapy*** : Irradiation of LN & spleen.
3. Splenectomy : for massive splenomegaly or hypersplenism.

Hairy Cell Leukemia

- ➢ It is a rare B-cell lymphoproliferative disorder associated with splenomegaly, pancytopenia and typical 'hairy cells' in blood and bone marrow.
- ➢ Mostly in middle-aged males, with a male-to-female ratio of 5:1
- ➢ Treatment :
  - o **Cladribine** (2- chlorodeoxyadenosine; CdA): infusion of 0.1mg/kg/d for 7 days.
  - o Splenectomy in severe cases.
  - o Supportive treatment : as usual.

LYMPHOMAS

Lymphomas are divided into Hodgkin's & Non- Hodgkin's lymphoma based on the histological presence of Reed-Sternberg cells.

Hodgkin's lymphoma

First described by Thomas Hodgkin in 1832

Hodgkin's disease is a malignant lymphoma characterized by Reed–Sternberg cells.

Incidence :

- Age : one major peak in the 20s and a second over age 50 years *(Bimodal age incidence)*
- Sex : higher incidence in ♂.

Risk factors:

- EBV (*Epstein-Barr virus*) : ↑ risk of HL in individuals with a history of infectious mononucleosis.
- Positive family history.

Clinical picture:

1) **LN enlargement** :
   - Painless, non-tender , discrete , rubbery lymphadenopathy.
   - Frequently cervical (60 - 80 %) , axillary in about 20% & inguinal in about 5%.
   - Mediastinal lymphadenopathy may produce local symptoms (e.g. bronchial or SVC compression) or direct extension (e.g. to pleura). Pleural effusions in 20%.
2) **Hepatosplenomegaly** : palpable splenomegaly in 10%, hepatomegaly 5%.
3) **Bone marrow involvement** : rare (1 - 4%)
   - Anemia.
   - Bleeding tendency.

4) **Systemic symptoms** : 30%

- Fever. (**P**el-Epstein fever , intermittent fever)
- Weight loss.
- Night sweats.
- Generalized **P**ruritus.
- Alcohol-induced lymph node **P**ain.

Clinical stages of Hodgkin's lymphoma : *(Ann Arbor classification)*

Stage I	Involvement of a single lymph node region.
Stage II	Involvement of 2 or more lymph node regions on the same side of the diaphragm.
Stage III	Involvement of lymph node regions on both sides of the diaphragm ± involvement of spleen.
Stage IV	Involvement of one or more extranodal sites (e.g. BM, liver)

Each stage is further subdivided into :

- A : Absence of systemic symptoms.
- B : Presence of systemic symptoms : fever, night sweats, weight loss

Investigations:

1) L.N. biopsy : *The most important diagnostic test*.
   - Presence of **Reed-Sternberg cells** surrounded by inflammatory cells.
   - Hodgkin's disease is histopathologically divided into 4 subtypes : MCQ
     1. Lymphocyte predominance : **Best** prognosis.
     2. Lymphocyte depletion : **Worst** prognosis.
     3. Nodular sclerosis : Most common in **adult**.
     4. Mixed cellularity : Most common in **children**.
2) Biopsy of other sites : may be necessary e.g. liver or bone marrow.

3) **Radiological** :

- ☞ Chest X ray.
- ☞ **CT** chest, abdomen and pelvis.
- ☞ Isotope bone scan, MRI may be necessary.

4) **Hematological & biochemical finding** :

- ➲ CBC :
  - o It may be normal.
  - o May show normochromic normocytic anemia.
  - o Lymphopenia.
  - o Neutrophilia , eosinophilia and thrombocytosis may be present.
- ➲ Liver function tests : ↑ transaminases may indicate liver involvement.
- ➲ ESR , LDH , Ca : ↑

Treatment :

I. Symptomatic treatment : e.g. blood transfusion , Antibiotics

II. Specific treatment :

- ➲ Radiotherapy : for early stages (I , IIA).
- ➲ Chemotherapy : for later stages.

Combination chemotherapy protocols : with or without radiotherapy.

- ✍ **ABVD** : **A**driamycin , **b**leomycin, **v**incristine, and **d**acarbazine.
- ✍ **MOPP** : **M**ustine , **O**ncovin (vincristine) , **p**rocarbazine ,**p**rednisolone.
- ✍ **COPP** : **C**yclophosphamide , **O**ncovin, **p**rocarbazine ,**p**rednisolone.

ABVD has a much lower risk of infertility than MOPP regimens and is not associated with increased risk of leukaemia.

III.Surgery : indicated in

- o Pressure manifestations.
- o Gastric lymphoma.

Non- Hodgkin's lymphoma

This includes all lymphomas without Reed-Sternberg cells.

Incidence :

- Age : old age (65 - 70 years).
- Sex : higher incidence in ♂. ☹

By Dr.Diaa Ahmed
Zagazig University

Risk factors:

- Infection :
  - ✓ EBV (*Epstein-Barr virus*) : Burkitt lymphoma.
  - ✓ Helicobacter pylori : gastric MALT lymphomas.
- Immunodeficiency : immunosuppressive drugs, transplantation, HIV
- Connective tissue disorders : e.g. Sjogren's syndrome. MCQ
- Chromosomal : translocation between the long arms of chromosomes 8 and 14.

Clinical picture:

As Hodgkin's disease but :

1) The diseases is **more aggressive** than Hodgkin's disease.
2) Hard lymphadenopathy.
3) Involved lymph nodes may be present also in the retroperitoneum, mesentery, and pelvis.
4) Abdominal pain & abdominal mass in **Burkitt lymphoma**.
5) Usually disseminated at the time of diagnosis.

	Hodgkin's lymphoma	*Non- Hodgkin's lymphoma*
Age	Young	Old
Site	Unicentric	Multicentric
Skin overlying	Normal	Red – hot – dilated veins
Consistency	Rubbery	Hard
Mobility	Mobile	Amalgamated (*confluent*)
prognosis	good	bad

Classification of NHL :

By Dr.Diaa Ahmed
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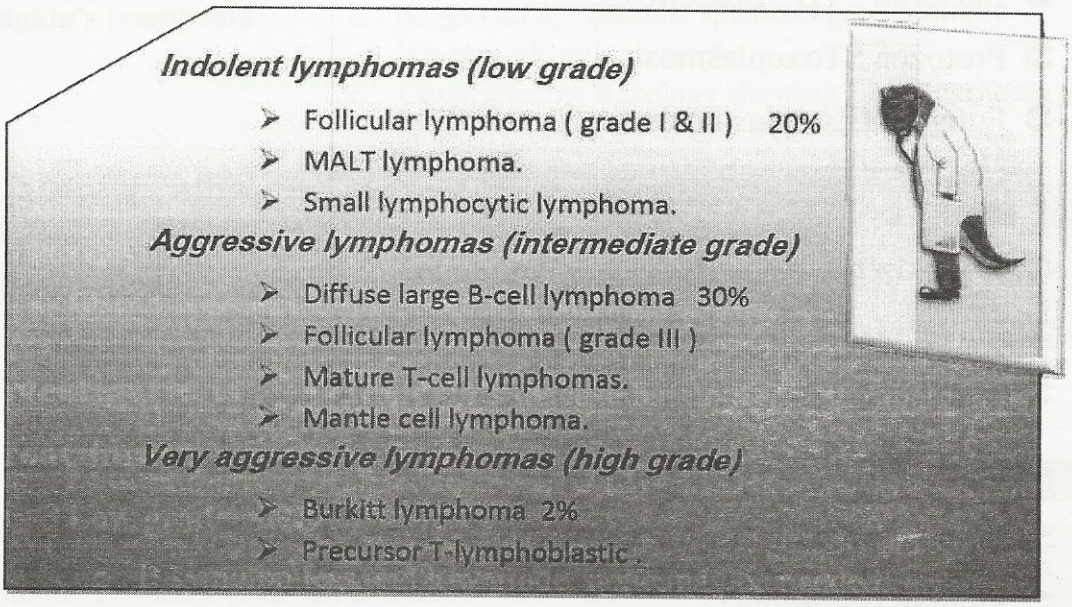
1) Indolent lymphomas (Low grade NHL).
2) Aggressive lymphomas (Intermediate grade NHL).
3) Very aggressive lymphomas (High grade NHL).



Burkitt lymphoma : ♂ : ♀ = 2 : 1 ☹

Presents with bulky central nodal disease ± extranodal involvement (typically in the abdomen), bone marrow and / or CNS involvement.

Investigations : **As Hodgkin's disease** but no Reed-Sternberg cells.

Treatment :

i. **Low grade NHL :**
   - If symptomless and low grade, none may be needed.
   - Radiotherapy to involved nodal regions.
   - Single agent chemotherapy e.g. chlorambucil.

ii. **Intermediate & high grade NHL :**
   - Combination chemotherapy : e.g. COPP (Cyclophosphamide , Oncovin, procarbazine , prednisolone)

iii. **Lymphoblastic NHL :** Treated as ALL (*Acute lymphoblastic leukemia*)

Causes of generalized Lymphadenopathy

1. Infection:

- Viral : Infectious mononucleosis , Hepatitis.
- Bacterial : TB , Brucellosis.
- Protozoa : Toxoplasmosis
- Fungal : Histoplasmosis.

2. Tumor :

- Hodgkin's & Non- Hodgkin's lymphoma.
- Leukemia : ALL , AML , CLL , CML.
- Metastasis

3. Immunologic :

- SLE.
- Sjogran syndrome.

4. Others :

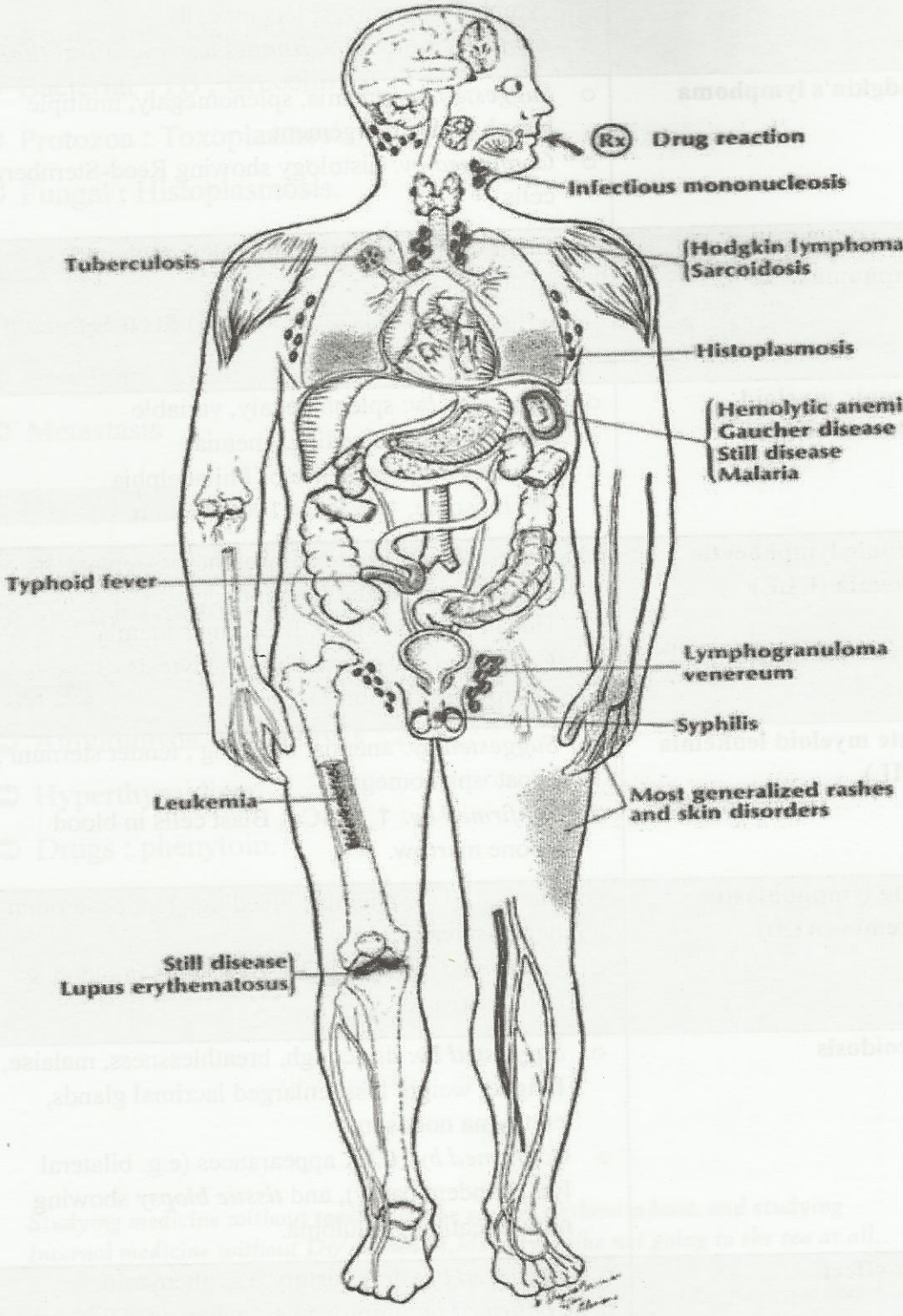
- Amyloidosis, Sarcoidosis ♫ ♫
- Hyperthyroidism.
- Drugs : phenytoin.

Studying medicine without teacher is like sailing without a boat, and studying Internal medicine without ***Dr/Ahmed M.Mowafy*** *is like not going to the sea at all.*

DR/Alsayed dawoud

Infectious mononucleosis (glandular fever) due to Epstein-Barr virus	○ *Suggested by:* very severe throat pain with enlarged tonsils covered with creamy membrane. Petechiae on palate. Profound malaise. Generalised lymphadenopathy, splenomegally. ○ *Confirmed by:* ***Paul-Bunnel*** test +ve. ***Viral titres.***
Hodgkin's lymphoma	○ *Suggested by:* anemia, splenomegaly, multiple lymph node enlargement. ○ *Confirmed by:* histology showing Reed-Sternberg cells.
Non-Hodgkin's lymphoma	○ *Suggested by:* anemia, multiple lymph node enlargement. ○ *Confirmed by:* histology with no Reed-Sternberg cells.
Chronic myeloid leukemia (CML)	○ *Suggested by:* splenomegaly, variable hepatomegaly, bleeding, anemia. ○ *Confirmed by:* presence of Philadelphia chromosome, ↑ WBC >100000/cmm.
Chronic lymphocytic leukemia (CLL)	○ *Suggested by:* anorexia, weight loss, enlarged rubbery non-tender lymph nodes. Hepatosplenomegaly, Bleeding , anemia. ○ *Confirmed by:* marked lymphocytosis. Bone marrow infiltration.
Acute myeloid leukemia (AML)	○ *Suggested by:* anemia, bleeding , tender sternum , hepatosplenomegaly. ○ *Confirmed by:* ↑ WBCs , Blast cells in blood &bone marrow.
Acute lymphoblastic leukemia (ALL)	○ *Suggested by:* anemia , bleeding , tender sternum , hepatosplenomegaly ○ *Confirmed by:* ↑ WBCs , Blast cells in blood & bone marrow.
Sarcoidosis	○ *Suggested by:* dry cough, breathlessness, malaise, fatigue, weight loss, enlarged lacrimal glands, erethyma nodosum. ○ *Confirmed by:* ***CXR*** appearances (e.g. bilateral lymphandenopathy), and ***tissue biopsy*** showing non-caseating granuloma.
Drug effect	○ *Suggested by:* drug history e.g. phenytoin. ○ *Confirmed by:* improvement when drug withdrawn.

Figure; illustrating causes of Generalized lymphadenopathy



HEMOSTASIS & BLEEDING

- Hemostasis means stopping of hemorrhage from injured blood vessels.
- It needs : (similar to building)

I. Blood vessel wall : (Base)

➲ Immediate recoil & vasoconstriction of injured vessel.

II. Platelets : (Stones)

➲ platelets adhesion and aggregation

III. Coagulation system : (Cement)

➲ **Coagulation factors :**

Factor I	**Fibrinogen**
Factor II	Prothrombin
Factor III	Tissue thromboplastin
Factor IV	Calcium
Factor V	Proaccelerin
Factor VII	Proconvertin
Factor VIII	Anti-hemophilic factor
Factor IX	Christmas factor
Factor X	Stuart Prower factor
Factor XI	Plasma thromboplastin antecedent
Factor XII	Hageman factor
Factor XIII	Fibrin stabilizing factor

➲ **Coagulation occurs through 2 pathways :** *see the figure*

1- Extrinsic pathway :

☑ It is a rapid process , triggered by trauma ⇨ Release of tissue thromboplastin (Factor III) ⇨ activation of factor VII ⇨ to common pathway *(activation of Factor X in presence of Ca)*

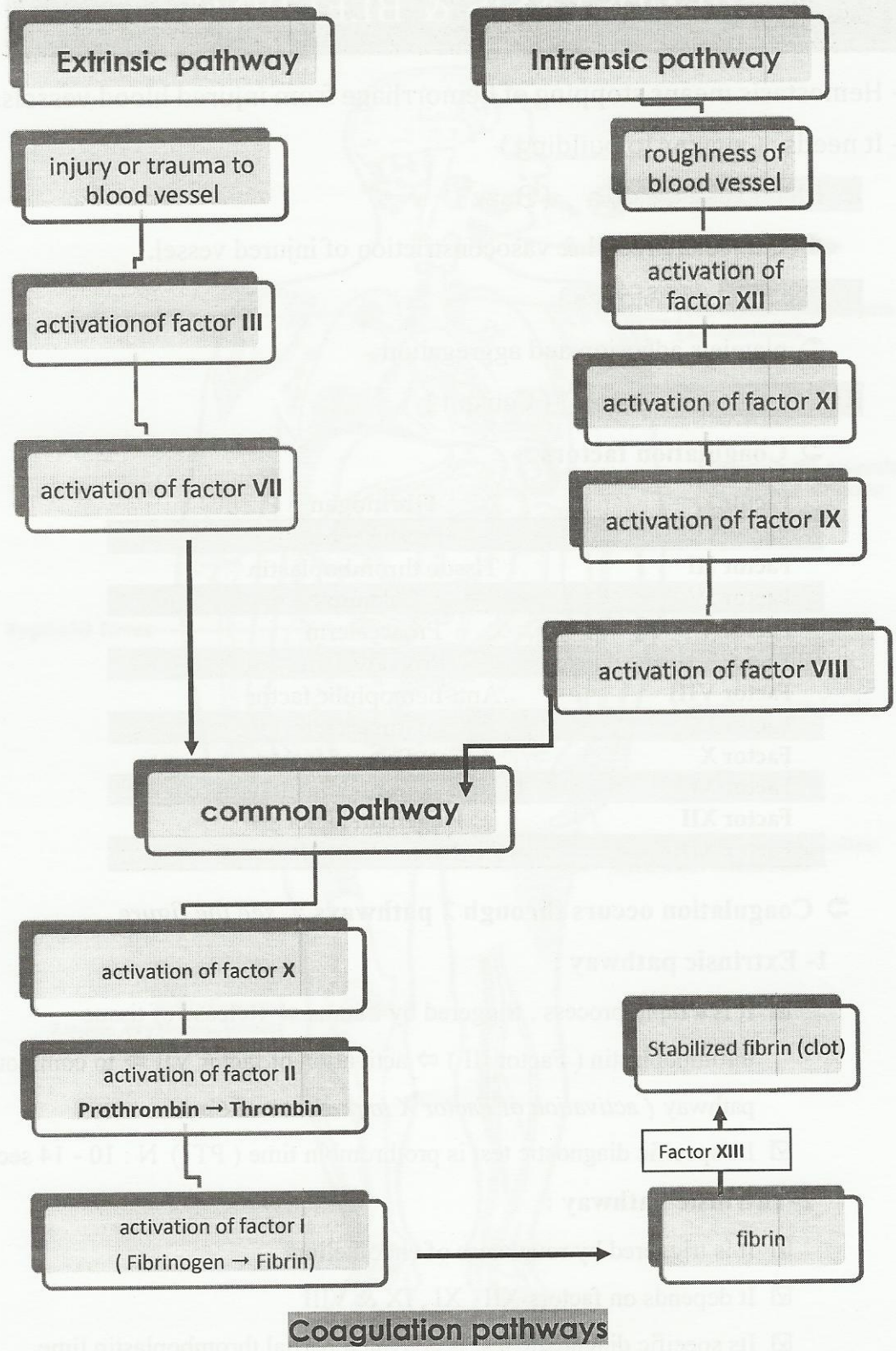
☑ Its specific diagnostic test is prothrombin time (PT) N : 10 - 14 sec.

2- Intrinsic pathway :

☑ It is triggered by roughness of endothelium.

☑ It depends on factors XII , XI , IX & VIII

☑ Its specific diagnostic test is activated partial thromboplastin time (APTT) , N : 30 - 40 sec.



Coagulation pathways

Hemostsis disorders

Hemostsis disorders fall into 3 groups:

I. **Vascular disorders.**

II. **Platelets disorders.**

III. **Coagulation disorders.**

I. Vascular disorders : (*Vascular purpura*)

A) **Acquired :**

- **I**mmune :
  - **Henoch–Schönlein (Anaphylactoid purpura) :** see below
  - Vasculitis e.g. SLE
- **I**nfection : Meningitis , Typhoid , IE.
- **I**atrogenic : Steroids , Sulphonamide.
- **I**diopathic (Purpura simplex) : especially in females over limbs & trunk . It resolves without treatment.
- **S**curvy (Vit C deficiency).
- **S**enile purpura.
- **M**alignancy.
- **M**enopause.

B) **Congenital :**

- Hereditary telangiectasia : *Osler–Weber–Rendu syndrome*

  Rare condition in which there are thin wall dilations in the wall of capillaries → recurrent haemorrhage and anemia.
- Ehlers-Danlos syndrome :

  ↑ skin elasticity & capillary fragility. ♫ ♫

II. Platelets disorders :

due to defects in either platelet number or platelet function.

a) **Platelet number (Thrombocytopenia)** : < 150,000/cmm

1. **Decreased production of platelets :**
   - Bone marrow failure.
   - Bone marrow infiltration : e.g. leukemia.
   - Vitamin B_{12} /folic acid deficiency.

2. **Increased destruction of platelets : 4 I** (normal or ↑ megakaryocyte)
   - **I**diopathic (*Immune*) thrombocytopenic purpura : (ITP)
   - **I**mmune : SLE.
   - **I**nfections : Epstein-Barr virus, HIV , Gram-negative septicemia
   - Hypersplen**i**sm ☺

3. **Increased consumption of platelets** : (normal or ↑ megakaryocyte)
   - Disseminated intravascular coagulation (DIC)
   - Thrombotic thrombocytopenic purpura (TTP)

b) **Platelet function (Thrombasthenia) :**

1. **Hereditary :**
   - Glanzmann's disease : Platelets are unable to aggregate.
   - von Willebrand's disease : reduced production of vWF factor.
2. **Acquired :**
   - Chronic renal failure : unknown mechanism.
   - Chronic liver disease.
   - Vitamin C deficiency (*Scurvy*)
   - Iatrogenic :
     - Anti-platelet : Aspirin.
     - Heparin.
     - Antibiotics: penicillin and cephalosporins.

Non thrombocytopenic purpura : Vascular purpura + Thrombasthenia

III. Coagulation disorders :

a) Congenital :

- Hemophilia A (classic hemophilia, factor VIII hemophilia)
- Hemophilia B (Christmas disease, factor IX hemophilia)
- Afibrinogenemia & dysfibrinogenemia.

b) Acquired :

- Liver cell failure.
- Vitamin K deficiency.
- Disseminated intravascular coagulation (DIC).
- Drugs : anti-coagulants.

Tests for purpura & Coagulation system

1. **Hess test** : (*capillary fragility test*)

   Detects vascular purpura. It may be +ve in other types of purpura.

2. **Bleeding time** : (2-7 minutes) obsolete investigation
   - Small incision is made & the wound is wicked with filter paper every 30 seconds until the fluid is clear.
   - Prolonged : in all types of purpura.

3. **Clotting time** : (5-10 minutes)
   - Indicator of the intrinsic pathway.
   - Not sensitive test as it take 4-5 minutes just to activate factor **XII**

4. **Activated Partial Thromboplastin Time** (aPPT , PTT) :
   - Normal : 30 - 40 seconds.
   - Used to evaluate the intrinsic coagulation system.
   - Used to monitor heparin therapy.
   - **Prolonged** : Heparin , Defect in the intrinsic pathway e.g. Hemophilia , DIC , von Willebrand disease.

5. **Prothrombin Time** (PT) :
   - Normal : 10 - 14 seconds
   - It is measured by adding tissue thromboplastin & Ca to the patient's plasma to activate extrinsic pathway.
   - Used to evaluate the extrinsic coagulation system.
   - Used to monitor oral anticoagulant therapy.
   - **Prolonged** : Oral anticoagulants , liver diseases , ↓ vit K , DIC
   - **INR** *(International Normalized Ratio)* :
     - INR = patient /control PT
     - Normal : 0.8 - 1.2
     - Therapeutic INR is 2 - 3

6. **Thrombin Time** (TT) :
   - Normal : 10 - 14 seconds.
   - It is performed by adding thrombin to the patient's plasma.
   - Measure of conversion of fibrinogen to fibrin.
   - **Prolonged** : Afibrinogenemia , Dysfibrinogenemia , DIC , Heparin.

I know not with what weapons World War III will be fought, but World War IV will be fought with sticks and stones.

Albert Einstein

Purpura

Definition:

Multiple spontaneous capillary bleeding in the skin & mucous membrane due to defect in platelets or in the wall of blood vessels.

Etiology :

I. **Vascular disorders.**

II. **Platelets disorders.**

Clinical picture :

- Bleeding : spontaneous & of short duration.
  - i. Skin :
    - Multiple petechiae , purpura.
      - ✓ Without raised edge in platelet disorders.
      - ✓ With raised edge in vascular disorders.
    - Small ecchymosis may occur.
  - ii. Mucous membrane : gum bleeding.
  - iii. Bleeding per orifices : epistaxis , menorrhagia , hematemesis.
  - iv. Internal organs : cerebral , retinal hemorrhage.
- Anemia.
- Features of the cause.

Petechiae	Ecchymosis
✓ Intradermal hemorrhage	✓ Subcautaneous hemorrhage
✓ Few mm	✓ Few cm
✓ Not raised	✓ Raised
✓ Disappear without color changes	✓ Color changes
✓ Not related to site of trauma	✓ Usually related to trauma

Henoch-Schönlein purpura

(*Anaphylactoid purpura* , *Allergic purpura*)

Definition :

- It is a type of small vessel vasculitis which occurs mainly in children.
- It is the most common cause of non thrombocytopenic purpura in children.
- Age peak : 2- 8 years.

Clinical picture :

The diagnosis of Henoch-Schönlein purpura depends on clinical findings and history. There is not a specific laboratory test for the disorder.

1) Skin : 100%

   Palpable Purpuric rash especially over buttocks & extensor surface of legs.

2) Joints : 75%
   - Migratory polyarthritis.
   - Particularly knees and ankles.

3) Abdominal pain & GIT bleeding due to mesenteric vasculitis. ?

4) Renal involvement : (*the worst prognosis*)
   - Focal glomerulonephritis.
   - Asymptomatic proteinuria & hematuria.

Investigations :

1) All investigations of bleeding tendency are normal except Hiss test may be +ve MCQ
2) Platelet count and function are normal.
3) Elevated serum IgA level is suggestive.
4) Skin biopsy : IgA deposits.

Treatment & prognosis :

- Spontaneous resolution within a month is commonest outcome in children.
- Chronic renal failure in 10% of cases.
- Steroids may improve the joints & gastrointestinal manifestations.

Immune thrombocytopenic purpura

(ITP)

Definition :

- It is an autoimmune disorder in which there is a destruction of the peripheral platelets by IgG autoantibodies.
- It is the most common cause of thrombocytopenia.

Types :

I. ***ITP in child*** : Acute type

- The condition is usually acute (< *6months*).
- Sex : equal.
- Frequently precipitated by viral infection.
- Usually self limited in most cases (90%)
- IgA level : normal.

II. ***ITP in adult :***

- The condition is usually chronic, with remissions and relapses.
- It may be associated with other autoimmune disorders e.g. SLE.
- Sex : ♀ > ♂ ☺
- IgA : less than normal.

Clinical picture :

a) General manifestations of purpura : *see before*

b) Spleen is not palpable & if enlarged never hugely enlarged. MCQ

Investigations :

I - ***Blood examination :***

✓ Thrombocytopenia :

platelet count < 150000/cmm & may be < 20,000/cmm in severe cases.

- ✓ Other counts are usually normal except for occasional mild anemia, which can be explained by bleeding or associated hemolysis.
- ✓ Platelet antibodies are present in most cases (65% of chronic cases)
- ✓ Bleeding time : prolonged
- ✓ Coagulation tests (CT , PT , APTT , TT) : normal

II- Bone marrow :

- ✓ The most important diagnostic test.
- ✓ Normal or increased megakaryocytes with defective budding.

Diagnostic criteria of ITP :

- ✓ **Isolated thrombocytopenia.**
- ✓ Other hematopoietic cell lines normal.
- ✓ No systemic illness.
- ✓ **Spleen not palpable.**
- ✓ Normal bone marrow with normal or increased megakaryocytes.

Treatment :

1) Most children do not require treatment as ITP is self limiting in most case. Just follow up for fear of intra-cerebral hemorrhage.

2) **Prednisone :**
   - ↓ Platelet antibody production and interferes with phagocytosis.
   - Dose : 2mg/kg/d orally for 2 weeks.
   - About 80% of patients will respond, and the platelet count will usually return to normal.

3) Splenectomy :
   - Splenectomy is a curative therapy for ITP as spleen is major site of platelet destruction.

- Indications :
  - ✓ Who fail to respond to prednisone.
  - ✓ Requiring high dose of prednisone.
- Precautions : Pneumococcal vaccine before & long acting penicillin after splenectomy.

4) Immunosuppressive agents :

- e.g. Azathioprine , cyclophosphamide or vincristine.
- Indication :
  - ✓ If no improvement after Splenectomy.
  - ✓ May be used with prednisolone to obtain an acceptable platelet count.

5) **IV immunoglobulin :** 1 g/kg for 1 or 2 days

- IV Ig blocks surface receptor of platelets (competitive inhibition of anti-platelets antibodies)
- Relatively non-toxic but expensive and the effect lasts only 1–2 weeks.
- Indications :
  - ✓ Refractory to other treatments.
  - ✓ Who require an urgent improvement for surgery and pregnancy.

6) **Platelets transfusion :**

- Use of platelets transfusion in ITP is ***a bad medicine*** as it destroyed by anti-platelets antibodies.
- May be indicated in life threatening conditions.

7) **Danazol :**

- An androgen that increase platelet count.
- May be used as alternative to prednisolone or in combination.
- Dose : 400–800mg/d for 1–3 months.
- Side effects: virilisation, weight gain and hepatotoxicity.

Coagulation disorders

Hemophilia

Types : *MCQ*

1. Hemophilia A : deficiency of factor VIII
2. Hemophilia B : deficiency of factor IX
3. Hemophilia C : deficiency of factor XI
4. Parahemophilia : deficiency of factor V

Hemophilia A

Definition :

- Congenital coagulation disorders caused by defective production of factor VIII.
- Hemophilia is an **X-linked recessive** disease, and as a rule only males are affected.

If a female carrier has a son, he has a 50% chance of having hemophilia, and a daughter has a 50% chance of being a carrier. All daughters of men with hemophilia are carriers and the sons are normal.

Do you understand anything ? ok ... read it again & you may understand ...

Degree :

- Severe : factor VIII < 1%
- Moderate : factor VIII 1–5%
- Mild : factor VIII > 5%.

Clinical picture : The disease affects only males ☹

☑ Bleeding :

- Since birth usually by trauma e.g. during circumcision *(Factor VIII received from the mother is enough for just one week)*.

- Ecchymosis (either spontaneously or after minor trauma)
- Intramuscular hematoma : following IM injections.
- **Hemoarthrosis** : spontaneous bleeding into joints (knees > elbows > ankles > hips > wrists) → fibrosis & deformity.
- Internal organs : GIT , CNS bleeding.
- Orificial : Epistaxis , bleeding gum , hematuria , hematemesis.
- Excessive bleeding after minor surgical procedure (tooth extraction)

☑ Neuropathy may occur due to pressure from hematoma.

☑ HBV, HCV and HIV may occur due to repeated blood transfusion.

Investigations :

☑ Reduced level or activity of factor VIIL.

☑ APTT : Prolonged .

☑ PT, bleeding time and vWF level are normal.

☑ Platelet count : normal.

☑ Radiological examination of joint : in hemoarthrosis.

Treatment :

1) General measures :
   - ☑ Avoid anti-platelet drugs e.g. Aspirin.
   - ☑ Avoid IM injections.
   - ☑ Avoid trauma.
   - ☑ Vaccinate against HBV.
2) Factor VIII concentrates are cornerstone of management.
3) Desmopressin (*Synthetic vasopressin*) : increases the release of factor VIII.
4) Fresh blood transfusion in severe bleeding.

Von Willebrand's disease (vWD)

- vWF plays a role in platelet adhesion to damaged subendothelium as well as stabilizing factor VIII) in plasma.
- So the deficiency of vWF results in :
  a) Platelet dysfunction.
  b) Hemophilia.
- Laboratory diagnosis : Like hemophilia but bleeding time is prolonged & impaired platelet function tests. *MCQ*
- Treatment : like hemophilia.

Disseminated intravascular coagulation

(DIC)

Definition :

It is an acquired coagulopathy in which there is widespread fibrin formation , resulting in consumption of platelets/coagulation factors & activation of fibrinolysis.

Etiology :

I. **Endothelial damage** ⇨ activation of intrinsic pathway
   - Infection : Gram –ve bacteria (e.g. meningococcus), Gram +ve bacteria (e.g. pneumococcus), anaerobes, TB ,viruses , …
   - Vascular : Malignant hypertension , MI.

II. **Trauma** ⇨ release of tissue factor ⇨ activation of extrinsic pathway
   - Obstetric complications : amniotic fluid embolism , retroplacental hemorrhage , IUFD , pre-eclampsia.
   - Crush injury , Thermal injury.
   - Leukemia : especially acute promyelocytic leukemia (M3) *MCQ*

Clinical picture : DIC leads to both bleeding and thrombosis

I. Clinical picture of the cause

II. Bleeding : (due to consumption of coagulation factors)

- Ecchymosis, petechiae, oozing from venepuncture sites.
- post-operative bleeding.

III. Thrombosis ⇨ Organ failure :

- Renal dysfunction.
- Cerebral dysfunction.
- ARDS.
- Skin necrosis.

Clinical types :

I. **Acute (uncompensated) DIC** :

- Rapid and extensive activation of coagulation & fibrinolysis with depletion of coagulant factors.
- Bleeding > thrombosis.

II. **Chronic (compensated) DIC** :

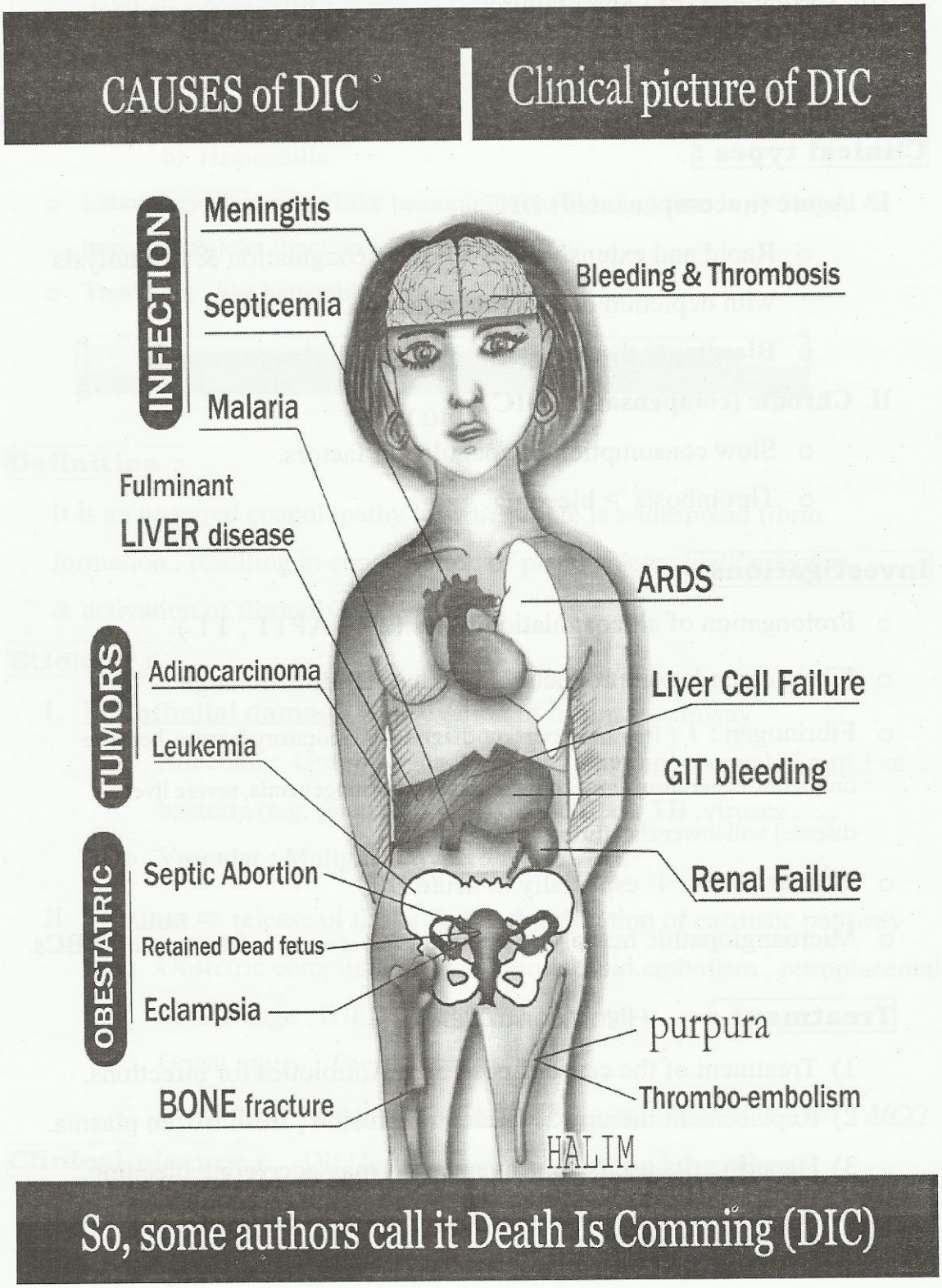
- Slow consumption of coagulation factors.
- Thrombosis > bleeding.

Investigations :

- Prolongation of all coagulation times (PT , APTT , TT)
- Fibrin degradation products (FDPs) & D- dimers : high
- Fibrinogen : ↓ (It is an important diagnostic laboratory feature, because only a few other disorders (congenital hypofibrinogenemia, severe liver disease) will lower the fibrinogen level).
- Platelet count : ↓ especially in acute DIC.
- Microangiopathic hemolytic anemia (25% of cases) : fragmented RBCs.

Treatment : Highly controversial

1) Treatment of the cause if possible : Antibiotics for infections.
2) Replacement therapy : Platelet transfusion , fresh frozen plasma.
3) Heparin : Its use is controversial , it may accelerate bleeding.
4) Antifibrinolytic (*epsilon-aminocaproic acid*) : Its use is controversial , it may accelerate microvascular clotting.


CAUSES of DIC
Clinical picture of DIC
INFECTION
Meningitis
Septicemia
Malaria
Fulminant
LIVER disease
TUMORS
Adinocarcinoma
Leukemia
OBESTATRIC
Septic Abortion
Retained Dead fetus
Eclampsia
BONE fracture
Bleeding & Thrombosis
ARDS
Liver Cell Failure
GIT bleeding
Renal Failure
purpura
Thrombo-embolism
HALIM
So, some authors call it Death Is Comming (DIC)

APPROACH TO A CASE OF BLEEDING TENDENCY

I. *Clinical approach :*

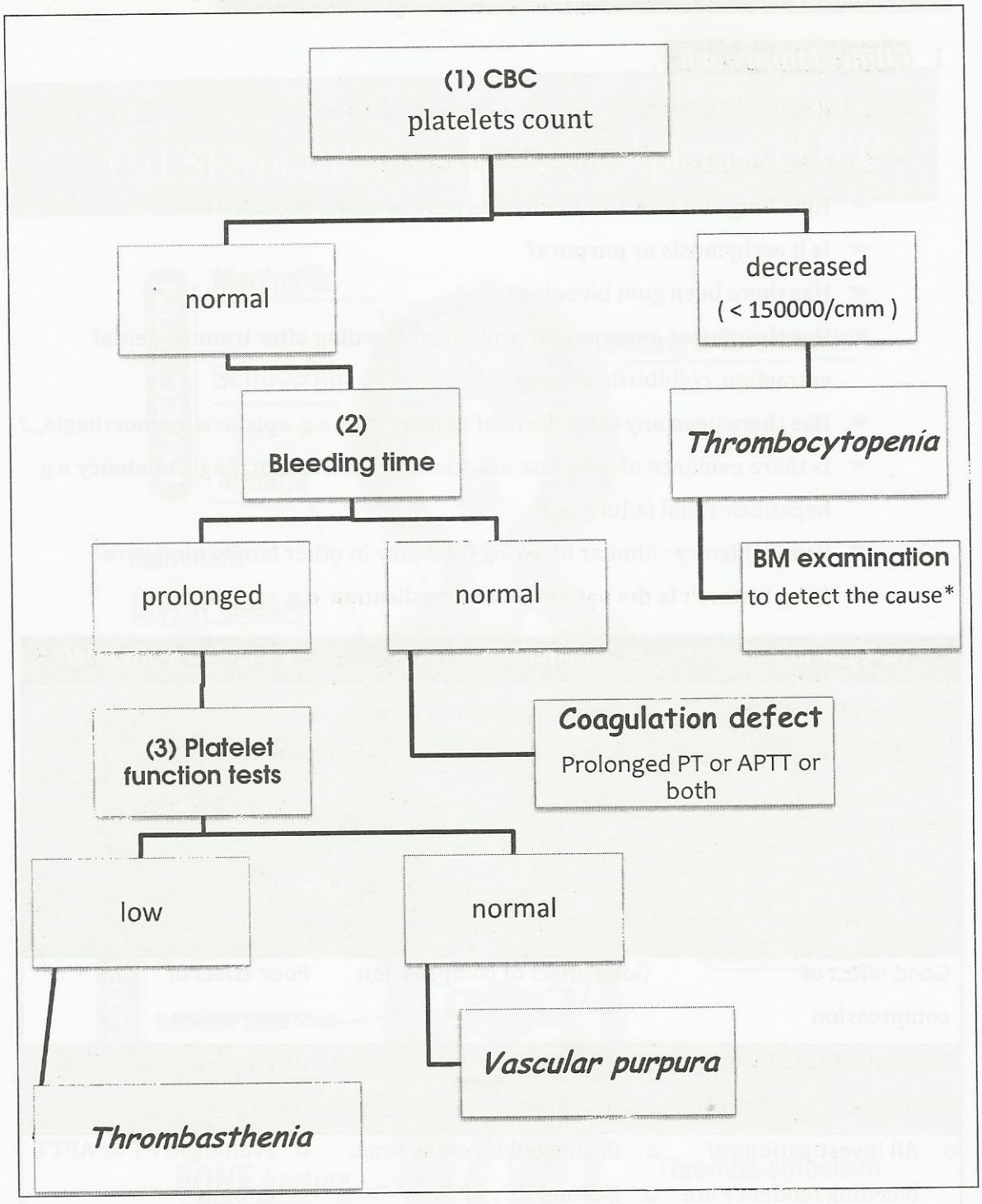
a) Etiology of bleeding : ..... see before

b) *Clinical features :* History & examination

- How long and how frequently has easy bruising occurred?
- Is it ecchymosis or purpura?
- Has there been gum bleeding?
- Has the patient experienced prolonged bleeding after trauma, dental extraction, childbirth or surgery?
- Has there been any other form of hemorrhage e.g. epistaxis, menorrhagia,..?
- Is there evidence of a disease associated with a hemorrhagic tendency e.g. hepatic or renal failure .... ?
- Family history : Similar bleeding tendency in other family members?
- **Drug history : Is the patient on any medication e.g. aspirin, ...**

Vascular disorders	Platelets disorders	Coagulation disorders
○ Petechiae with raised edge (palpable purpura)	○ Petechiae without raised edge . ○ bleeding gums, epistaxis or more serious life-threatening hemorrhage. ○ Small ecchymosis.	○ Ecchymosis ○ Hemoarthrosis ○ Hematomas
Good effect of compression	Good effect of compression	Poor effect of compression
Bleeding is usually post traumatic	Bleeding is usually spontaneous	Bleeding is usually post traumatic
○ All investigations of bleeding tendency are normal except Hiss test ○ Platelet count and function are normal.	○ Prolonged bleeding time. ○ Normal PT , APTT	○ Prolonged PT or APTT or both ○ Normal bleeding time. ○ Assay of coagulation factors is important.

II. *Investigations for a case of bleeding :*



* Bone marrow examination : is the definitive investigation in all patients with moderate or severe thrombocytopenia :

a) Decreased megakaryocytes : bone marrow failure.
b) Normal or increased megakaryocytes : ITP , Hypersplenism , ...

POLYCYTHEMIA

(*Erythrocytosis*)

By Dr.Diaa Ahmed
Zagazig University

Definition :

Increase in red blood cell count and hematocrit.

Types :

I. Polycythemia rubra vera (PV) : primary myeloproliferative disorder.

II. Secondary polycythemia : *(due to ↑ erythropoietin)* **5 C** ☺

- **C**hronic hypoxia : COPD , Cyanotic congenital heart diseases .....
- **C**ancer : Paramalignant syndrome e.g. lung cancer , hepatoma.
- **C**ushing's syndrome.
- **C**ortisone therapy.
- **K**idney : Polycystic kidneys , Renal artery stenosis.

III. Relative polycythemia : *(pseudopolycythemia , Gaisbock's syndrome)*

- Decrease in plasma volume with normal RBC mass.
- Due to diuretic therapy or dehydration.

Clinical picture of polycythemia vera :

1) **P**lethora and engorged retinal veins.
2) **B**lood hyperviscosity :
   - LCOP e.g. headache, dizziness, blurred vision, fatigue…
   - Hypertension & Congestive heart failure may occur.
   - Thrombosis.
3) **P**alpable spleen.
4) **P**ruritus especially following a warm shower. It is related to histamine release due to basophilia .

Complications :

- Thrombosis.
- Over time, polycythemia vera may convert to myelofibrosis or to chronic myeloid leukemia.

Investigations :

1) **CBC :**
   - ➲ RBCs : ↑ (> 6000,000 / cmm).
   - ➲ RBC mass > 36 ml/kg (♂) & > 32 (♀)
   - ➲ Hematocrit : ↑
   - ➲ WBCs & platelets : ↑ in polycythemia vera . *(rare in other causes of polycythemia).*
   - ➲ ESR : ↓
2) **Arterial oxygen saturation :** to detect chronic hypoxia.
3) **Bone marrow examination :**
   - o Hypercellularity of all BM elements especially erythroid cells.
   - o Normal in secondary polycythemia.
4) **Others :**
   - o Vitamin B_{12} : ↑ because of increased levels of transcobalamin III (secreted by white blood cells).
   - o Uric acid: ↑

The diagnostic criteria of polycythemia rubra vera (PV)

- **A1** : ↑ RBC mass > 36 ml/kg in ♂ , > 32 in ♀ or Hematocrit ≥ 60%
- **A2** : Normal O2 saturation (*to exclude hypoxia*).
- **A3** : Palpable splenomegaly.
- **A4** : Abnormal BM karyotype.
- **B1** : Thrombocytosis (platelet count > 400,000/cmm)
- **B2** : TLC > 12.000/cmm
- **B3** : High leucocytic alkaline phosphatase.
- **B4** : Reduced serum erythropoietin.

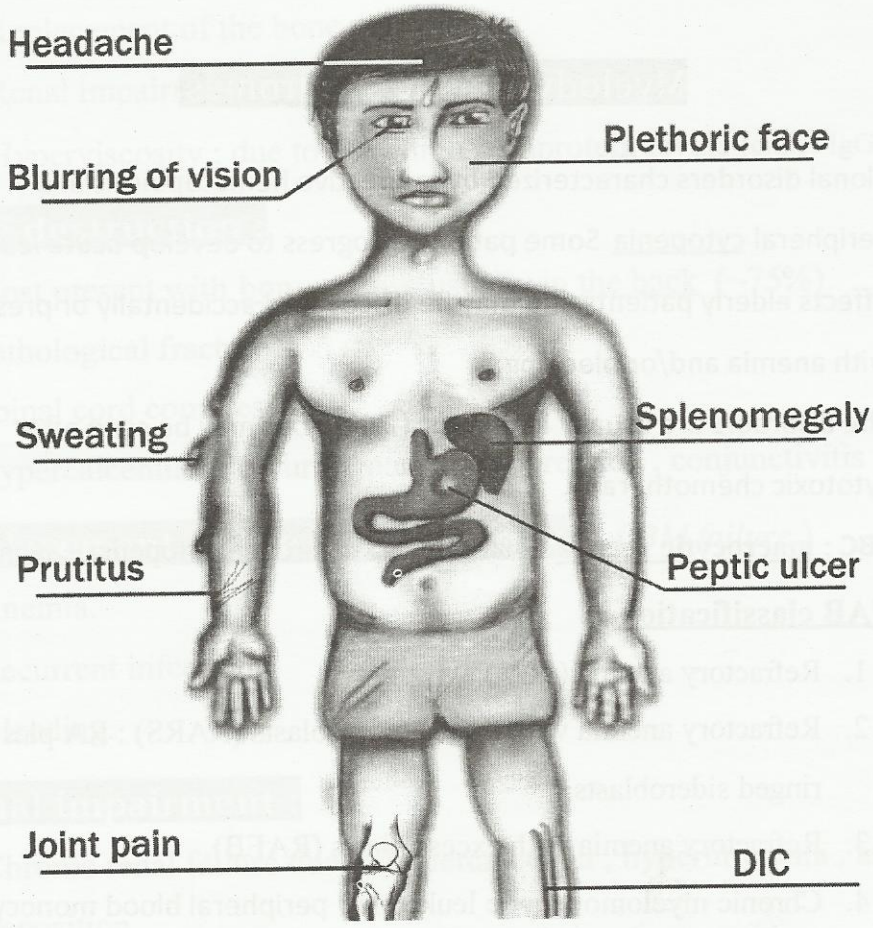
Diagnosis of PV :

☞ A1 + A2 + A3 or A4 ☞ A1 + A2 + two of B

Treatment of polycythemia vera :

1) Supportive treatment :
   - Adequate fluid intake and avoid dehydration.
   - Allopurinol for hyperuricemia.
2) **Repeated venesection** : to keep hematocrit below 50%.
3) **Hydroxyurea** : myelosuppressive agent.
4) Radioactive phosphorus (P^{32}) and busulfan.
5) Treatment of complications : e.g. Aspirin to prevent thrombosis.

SYMPTOMS OF POLYCYTHEMIA | **SIGNS OF POLYCYTHEMIA**



Myeloproliferative syndromes

Definition : *Clonal abnormalities of the hematopoietic stem cell.*

1) Polycythemia vera.
2) Myelofibrosis.
3) Essential thrombocytosis.
4) Chronic myeloid leukemia.

	White Count	Hematocrit	Platelet Count	Red Cell Morphology
Chronic myeloid leukemia	↑↑	N	N or ↑	N
Myelofibrosis	N or ↓ or↑	N or ↓	↓ or N or ↑	Abnormal
Polycythemia vera	N or ↑	↑	N or ↑	N
Essential thrombocytosis	N or ↑	N	↑↑	N

Myelodysplastic syndromes

- Clonal disorders characterized by ineffective hematopoiesis and peripheral cytopenia. Some patients progress to develop *acute leukemia*.
- Affects elderly patients and may be discovered accidentally or present with anemia and/or bleeding.
- The disorders are usually idiopathic (70%) but may be seen after cytotoxic chemotherapy.
- **CBC : macrocytic anemia** ± neutropenia ± thrombocytopenia ± monocytosis.
- **FAB classification :**
  1. Refractory anemia (RA).
  2. Refractory anemia with ringed sideroblasts (RARS) : RA plus ringed sideroblasts.
  3. Refractory anemia with excess blasts (RAEB).
  4. Chronic myelomonocytic leukemia : peripheral blood monocytosis.

MULTIPLE MYELOMA

(*Myelomatosis*)

Definition :

Multiple myeloma is a clonal B-cell malignancy characterized by proliferation of plasma cells that accumulate mainly within bone marrow and usually secrete paraprotein, mainly IgG or IgA and rarely IgD.

Clinical picture :

- Multiple myeloma is a disease of elderly and appears usually around the age of 60 years & more common in ♂. ☹
- The clinical manifestations are due to :
  1. Bone destruction.
  2. Replacement of the bone marrow.
  3. Renal impairment.
  4. Hyperviscosity : due to very high paraprotein levels (either IgG or IgA).

1- **Bone destruction :**

- Most present with **bony pain** : usually in the back (~75%)
- Pathological fracture.
- Spinal cord compression.
- Hypercalcemia : Polyuria , nausea , depression , conjunctivitis …

2- **Replacement of the bone marrow :** (*BM failure*)

- Anemia.
- Recurrent infection.
- Bleeding.

3- **Renal impairment :**

Chronic renal failure due to hypercalcemia , hyperuricemia , amyloid deposition .

4- **Hyperviscosity :** (slow circulation)

Fatigue , Headache , Blurring of vision.

Investigations :

1) Normochromic normocytic anemia , may show rouleaux.
2) **ESR :** always high.
3) **Serum protein electrophoresis : finding of paraproteins.**
4) Bone marrow examination : plasma cell infiltration.
5) Urine examination : may be +ve for Bence Jones protein.
6) X-ray bone : pathological fracture or lytic lesions.
7) Biochemical : ↑ urea , creatinine , Ca with normal alkaline phosphatase.

Diagnostic criteria for multiple myeloma

- Paraprotein in serum and/or urine.
- Replacement of bone marrow by malignant plasma cells.
- Myeloma-related organ damage e.g. bone pain, CRF ..

Suspect MM in a patient >50 with bone pain, anemia, recurrent infection, renal impairment, hypercalcemia , neuropathy & ↑ ESR.

Treatment :

I. Supportive therapy :

- Bone disease : local radiotherapy for localized pain , bisphosphonate.
- Allopurinol : to prevent urate nephropathy.
- Antibiotics : for infections.
- Anemia : blood transfusion , erythropoietin.
- Hyperviscosity syndrome : plasmapheresis.

II. Specific treatment :

- Melphalan and prednisolone.
- Combination chemotherapy :

VAD regimen (**V**incristine, **A**driamycin and **D**examethasone).

THE SPLEEN

Causes of splenomegaly :

I. **Infection** :
- **Viral** : EBV, CMV, hepatitis.
- **Bacterial** : SBE, TB , Salmonella , Brucella.
- **Protozoal/parasitic**: Bilharziasis, Malaria, toxoplasmosis, leishmaniasis.

II. **Blood disorders** :

a) **Chronic hemolytic anemias :**
- Autoimmune hemolytic anemia.
- Hereditary spherocytosis.
- Thalassaemia.

b) **Myeloproliferative disorders :**
- Myelofibrosis.
- CML.
- polycythemia rubra vera.
- Essential thrombocythemia.

c) **Lymphoproliferative disorders :**
- CLL
- Hairy cell leukemia.
- Most lymphomas.

III. **Autoimmune disorders** :
- SLE.
- Felty's syndrome.
- Rheumatoid arthritis.

IV. **Circulatory disorders :** Portal hypertension , portal vein thrombosis.

V. **Infiltration** :
- Gaucher's disease : genetic disease in which lipid accumulates in cells & organs . It is the most common *lysosomal storage disease*.
- Amyloidosis.

DD of just palpable spleen :

- Typhoid.
- Infective endocarditis.
- Hepatitis.
- Brucellosis.

DD of huge splenomegaly :

- Bilharziasis.
- CML.
- Thalassemia.
- Myelofibrosis.
- Gaucher's disease.
- Malaria.
- Hairy cell leukemia.
- Polycythemia.
- Myelosclerosis.
- Kala Azar (Leishmaniasis)

Hypersplenism

Definition :

Excessive splenic function, which lead to accelerated destruction of one or more of the three elements of blood.

Causes :

1. Primary : no cause of splenomegaly is detected.
2. Secondary : on top of enlarged spleen e.g. Bilharziasis , Malaria …

NB : Hypersplenism can occur in absence of splenomegaly, as in chronic ITP.

Mechanisms :

1. Mechanical obstruction inside the splenic bulb (Sequestration).
2. Formation of autoantibodies against the blood cells.
3. Secretion of certain agents which inhibit the release of cells from bone marrow.

Diagnostic criteria :

1. Splenomegaly.
2. Peripheral cytopenia. (*of one or more cell lines*)
3. Normal or hypercellular bone marrow.
4. Improvement after splenectomy.
5. Radioactive RBCs : phagocytosed inside the spleen.

Indications of splenectomy

1. Blood diseases :

- Hypersplenism : bilharziasis , lymphoma.
- Spherocytosis.
- ITP : after failure of steroid therapy.

2. Traumatic : second commonest indication. But the commonest indication abroad.

3. Others :

- ✓ Tumors/cysts , splenic abscess.
- ✓ As a part of other operations : Radical gastrectomy , Radical pancreatectomy.

Hematological & immune changes after splenectomy :

- ☞ Howell-Jolly bodies (*Nuclear remnants in the red cells*).
- ☞ Neutrophilia in response to infection.
- ☞ Increased platelet count and occasionally spherocytes with increased aniso- and poikilocytosis.
- ☞ Decreased IgM level.

Causes of hyposplenism 5S

1) **S**plenectomy : see above
2) **S**ickle cell disease.
3) **C**oeliac disease.
4) **C**ongenital asplenism (rare)
5) E**s**sential thrombocythemia.

Infection prophylaxis necessary in hyposplenism :

- ➢ Pneumococcal vaccine : is required at least 2 weeks before planned splenectomy, if the operation is unplanned then it should be given as soon as possible afterwards.
- ➢ Meningococcal & H. influenza vaccines.
- ➢ Post operatively , prophylactic long-term penicillin V 500 mg/12h.

BLOOD TRANSFUSION

Indications :

1. To restore blood volume
2. Acute hemorrhage *external or internal*
3. Operative & Post operative replacement
4. Severe burn
5. To provide deficient blood elements
6. Packed RBCs as in patient with severe anemia
7. Fresh frozen plasma → haemophilia , liver cell failure , DIC
8. Platelets concentrate → acute leukemia , thrombocytopenia
9. Cryoprecipitate → haemophilia.
10. Albumen → hypoalbumenemia.

Test the blood for :

1. ABO antigen.
2. Rh antigen.
3. Coomb`s test.

Complication :

ACUTE (WITHIN 1ST 72 HRS)

1) Hemolytic transfusion reaction :

Due to incompatible blood transfusion → destruction of donor RBCs by the recipient Ab.

Clinical picture:

Symptoms :

- Fever with rigor , Headache , Malaise & Anorexia. (FHMA)
- Chest pain & Dyspnea.
- Nausea & Vomiting

Signs:

- Fever
- Tachycardia
- Cyanosis
- Hypotension
- Oliguria & hemoglobinuria . Later on renal failure.

If patient is under anaesthesia or comatosed, incompatibility is suspected by :

- progressive unexplained hypotension
- Unexplained tachycardia

Treatment of haemolytic reaction:

- ☑ Stop the transfusion.
- ☑ IV fluid.
- ☑ Alkalinisation of urine.

2) Febrile non haemolytic reaction :

due to presence of leucocyte antibodies against donor leucocytes.

3) Allergic reaction.

4) ARDS.

5) Acidosis.

6) Hyperkalemia & hypocalcemia.

7) Circulatory overload (***heart failure***).

8) Hypothermia.

9) Bleeding tendency due to :

- Dilution of the patient blood platelets
- Deficient clotting factors

10) Air embolism.

11) Thrombophilibitis at the site of injection.

12) Acidosis

DELAYED (AFTER 72 HRS)

1) Delayed hemolysis.
2) Post-transfusion purpura.
3) Iron overload.
4) Transmission of diseases as :
   - AIDS
   - HBV , HCV.
   - Brucellosis
   - CMV
   - Malaria

Complications in the donor :

1) Anemia.
2) Complications of repeated venous puncture.

Red Cell Transfusions :

Acute Blood Loss :

Healthy persons can usually tolerate up to 30% blood loss without transfusion.

- Hgb > 10 g/dL, transfusion rarely indicated.
- Hgb 7–10 g/dL, transfusion based on clinical symptoms, unless patient has severe medical problems (eg, IHD , severe COPD).
- Hgb < 7 g/dL, transfusion usually needed.

Chronic anemia :

RBC Transfusion Formula :

$$\text{Volume of cells} = \frac{\text{Total blood volume of the patient X (desired HCT} - \text{Actual HCT)}}{HCT\ of\ transfusion\ product}$$

where total blood volume is 70 mL/kg in adults, 80 mL/kg in children. The HCT of PRBC is approximately 70%, and that of whole blood is approximately 40%.

COLLECTIONS

Morphology & Differential Diagnosis :

- **Poikilocytosis** (irregular shape) : in megaloblastic anemia.
- **Anisocytosis** (irregular RBCs size) : in megaloblastic anemia.
- **Basophilic Stippling** (punctuate basophilia) : Lead , thalassemia, severe anemia.
- **Heinz bodies** : Drug-induced hemolysis
- **Helmet Cells** : Microangiopathic hemolysis , hemolytic transfusion reaction, transplant rejection.
- **Howell-Jolly bodies** (small round nuclear remnants) : post splenectomy , megaloblastic anemia.
- **Nucleated RBCs** : Severe bone marrow stress (eg, hemorrhage, hemolysis, hypoxia), marrow replacement by tumor, extramedullary hematopoiesis.
- **Polychromasia** : A bluish red cell suggests reticulocytes.
- **Sickling** : Sickle cell anemia
- **Schistocytes** : DIC, microangiopathic anemia.
- **Spherocytes** : Hereditary spherocytosis, immune hemolysis, severe burns, ABO transfusion reaction.
- **Target Cells** (Leptocytes): Thalassemia, hemoglobinopathies, liver disease, any hypochromic anemia.

WBC Morphology & Differential Diagnosis :

Auer Rods : AML

Dohle Inclusion Bodies : Severe infection, malignancy, pregnancy.

Hypersegmentation : Megaloblastic anemia.

Toxic Granulation : Severe illness (sepsis, burn, high fever).

Causes of raised ESR :

- Pregnancy : maximal in 3rd trimester.
- Infections : Acute and chronic infections e.g. TB
- Collagen disorders : Rheumatoid, SLE, polymyalgia rheumatica, vasculitis..
- Inflammatory bowel disease, sarcoidosis, post-MI.
- Neoplastic conditions : NHL, Hodgkin's disease , Multiple myeloma .

Causes of hypercoagulability :

I. Acquired :

- Cancer.
- Inflammatory disorders : ulcerative colitis.
- Myeloproliferative disorders.
- Postoperative.
- Estrogens, pregnancy.
- Anticardiolipin antibodies (anti-phospholipid syndrome)
- Paroxysmal nocturnal hemoglobinuria.

II. Congenital :

- Antithrombin III deficiency.
- Protein C or S deficiency.
- Dysfibrinogenemia.
- Abnormal plasminogen.

Indications for allogeneic stem cell transplantation (SCT) :

- Relapsed AML , ALL.
- Severe aplastic anemia.
- Chronic myeloid leukemia.
- Myelodysplasia.
- Multiple myeloma (stage II/III).
- Primary immunodeficiency syndromes.
- Thalassaemia major.
- Sickle cell disease.
- Relapsed aggressive histology NHL & Hodgkin's lymphoma.

Causes of ↑ reticulocyte counts : Bone marrow stimulation due to :

- Reticulocytes represent an intermediate maturation stage in marrow between the nucleated red cell and the mature red cell. (*No nucleus but retain some nucleic acid*).

- **Bleeding.**
- **Hemolysis.**
- Response to iron , folate or vit B_{12} therapy.
- Myeloproliferative disorders.
- Marrow recovery following chemotherapy or radiotherapy.
- Infection.
- Inflammation.
- Erythropoietin administration.

If the reticulocytes count is high , blood loss or hemolysis is likely to be a cause of anemia.

Differences between heparin and oral anticoagulants :

	Heparin	Oral anticoagulant (warfarin)
Source	- Natural. It is formed with histamine in mast cells.	- Synthetic
Pharmacological actions	- Anticoagulant in vivo and vitro - Hypolipidaemic effect	- Anticoagulant only in vivo
Pharmacokinetics	- Ineffective by mouth because it is precipitated by acid - Not cross the placenta or secreted in breast milk	- Rapidly absorbed from GIT cross the placenta and secreted in breast milk
Mechanism	- Its action depends on the presence of heparin cofactor (antithrombin III) in plasma - It markedly activates antithrombin III that inhibits several activated clotting factors (mainly Xa, IIa, XIIIa)	- They compete with vit.K to inhibit its utilization in the formation of prothrombin and factors VII, IX, X by the liver. - This is through inhibition of vit.K-epoxide reductase enzyme preventing the reduction of vit.K to its active form.
Route	- Parentral	- Oral ☺
Dose	5000-10,000 units I.V followed by 5000 units/8 hours.	- Initial dose:10 mg (loading for 2 days) - Maintenance:2-15 mg /D according to prothrombin activity.
Control of therapy	- Blood coagulation time, it is kept at 2-3 times its normal value - Activated partial thromboplastin time (APTT) should be kept at 2 times normal value	- Dose is adjusted according to prothrombin time or INR which should be kept in the range 2-3 the normal value with maintenance therapy.
Onset	- Immediate after I.V injection	- Delay, take about 1-3 days
Antidote	- Protamine sulphate i.v usually 1mg is required to antagonize 100 units heparin.	- Vit.K dose of 50 mg I.V

What are the major differences between standard heparin and LMWH?

- LMWH has a longer half-life and thus can be administrated once daily.
- LMWH gives more predictable anticoagulant response at high doses and thus can be administrated without monitoring (serial PTT)
- LMWH produces less bleeding complications than standard heparin.

CASES

A 67-year-old woman is seen for complaints of mild memory loss and fatigue. On evaluation, she is found to have an anemia, which is characterized by the following laboratory values: white blood cell count, 5,200/mm^3; hemoglobin, 9.1 g/dL; hematocrit, 26.9%; MCV, 101 fL; reticulocytes, less than 1%; and platelets, 154000/mm^3. Her serum cobalamin level is 260 pg/mL and her folate, thyroid-stimulating hormone, and liver function tests are normal.

- How would you further evaluate this patient's anemia?
- On the basis of the laboratory results so far, what test, or tests, might be helpful in diagnosing the cause of this patient's anemia?
- Why might such a patient be deficient in cobalamin?

- **How would you further evaluate this patient's anemia ?**

  Serum cobalamin and folate levels should be determined. In addition, a search for both alcohol abuse and liver disease should be undertaken and hypothyroidism ruled out. If none of these is found to be a likely cause, other reasons for the anemia (refractory or aplastic anemia) should be explored. A peripheral blood smear should be examined for possible clues such as hypersegmented polymorphonuclear leukocytes (seen in cobalamin deficiency) or target cells (seen in liver disease).

- **On the basis of the laboratory results so far, what test, or tests, might be helpful in diagnosing the cause of this patient's anemia?**

  This patient likely has cobalamin deficiency, although her serum cobalamin level of 260 pg/mL is within the normal range. Because studies have shown that such deficiency results in methylmalonic aciduria and homocystinemia, these metabolic substrates should be measured in this patient. Other testing that might be considered includes a Schilling test or measurement of anti-intrinsic factor antibodies.

- **Why might such a patient be deficient in cobalamin?**

  There are various causes of cobalamin deficiency. It can stem from the ingestion of insufficient animal protein, as seen in true vegetarians. Failure to release cobalamin from food binders or failure to secrete intrinsic factor results in pernicious anemia. Failure to absorb the intrinsic factor-cobalamin complex in the distal ileum, as occurs in patients who have undergone an ileal resection can also lead to cobalamin deficiency.

A 35-year-old woman presents to the emergency room complaining of a nosebleed that has persisted for several hours. She denies a history of previous bleeding , although she has noticed some increased bruising during the last week and the appearance of a small, purplish rash on her feet and ankles. She denies any excessive bleeding with the delivery of her three children and has not undergone any surgical procedures. She denies taking aspirin, although she has taken acetaminophen for relief of a mild backache, and is on no other medications. On review of her symptoms, she denies arthralgias, arthritis, fevers, cold symptoms, or other infectious symptoms; she has been in good health until now. On examination, she is found to be well developed and in no distress. There is some fresh as well as dried blood obscuring the nasal mucosa; she has no conjunctival hemorrhages but does have palatal petechiae. Her spleen is not palpable but there is a petechial rash around both ankles. Her nosebleed requires nasal packing for control.

The following initial laboratory values are found: white blood cell count, 6,700/mm^3 with a normal differential; hemoglobin, 14.2 g/dL; hematocrit, 42.2%; MCV, 85 fl ; platelets, 50,000/mm^3; PT, 11.5 seconds and PTT, 28 seconds.

- What would you do next to evaluate this patient's bleeding?
- What results would you expect from the further evaluation of this patient's bleeding?
- What therapy would you institute in this patient?

- **What would you do next to evaluate this patient's bleeding?**

  Her clinical picture is consistent with that of **ITP** : normal coagulation findings and complete blood count, except for the platelet count, and the absence of other physical findings such as an enlarged spleen.
  bone marrow biopsy would show an increased or normal number of megakaryocytes. Some clinicians may choose to treat for presumptive ITP and evaluate the patient in 24 hours.

- **What therapy would you institute in this patient?**

  Platelet transfusions would not be helpful in this patient and might even accelerate the destructive process. Prednisone treatment (60 to 100 mg per day) should be initiated once bone marrow findings confirm the diagnosis or if the patient is treated empirically.

A 37-year-old man is seen because of lack of energy, night sweats, and poor appetite with a sensation of fullness after eating even very small amounts of food. Physical examination reveals signs of anemia, splenomegaly, and the existence of petechiae. A complete blood count is performed and yields the following findings: hematocrit, 25%; platelets, 300,000/mm^3, and white blood cells, 72,000/mm^3. A bone marrow biopsy is performed and the specimen is found to exhibit a granulocytic - erythroid ratio of 10:1 with 100% cellularity and 1% blastocytes.

- What is the differential diagnosis in this patient, based on the physical examination findings?
- On the basis of the hematologic findings, what hematopoietic abnormalities would you expect in this patient with suspected CML?
- What do the bone marrow findings indicate in this patient?
- What would be the most specific test for establishing the diagnosis of CML in this patient?
- If the patient is started on single-agent chemotherapy, what would be the likely effect?

- **What is the differential diagnosis in this patient, based on the physical examination findings?**

  - When the diagnosis of CML is considered, other possibilities, such as a solid cancer, lymphomas, and chronic infections must be excluded. These other diseases may cause a leukemoid reaction by increased stimulation of normal myelopoiesis. Usually a leukemoid reaction results in a white blood cell count of less than 100,000/mm^3, and less than 10% of cells are myelocytes or more immature forms.
  - **Splenomegaly** is almost the rule in patients with CML, and it is the source of poor appetite and upper abdominal pain, such as that seen in this patient. Because normal hematopoiesis is suppressed, the patient could exhibit the signs and symptoms of anemia, such as headache, palpitations, pallor, and cardiac failure.
  Finally, petechiae, although possible, are not very frequent findings in patients with CML.

- **On the basis of the hematologic findings, what hematopoietic abnormalities would you expect in this patient with suspected CML ?**

  Normal hematopoiesis is suppressed by the leukemic activity in the bone marrow, leading to a decreased number of red blood cells, as well as decreased hemoglobin level and hematocrit. Typically, the anemia of CML is normochromic normocytic. Although immature, most of the white blood cells look morphologically normal, and mature neutrophils, band forms,

metamyelocytes, and myelocytes constitute most of the white blood cells in this patient. Another characteristic finding is an increased number of basophils. If most of the cells are blasts, this indicates acute leukemia in most cases, although it can also indicate that the patient is in the blastic phase of CML.

- **What do the bone marrow findings indicate in this patient ?**

  The bone marrow findings are consistent with a diagnosis of CML, and bone marrow biopsy constitutes an important part of the diagnostic evaluation in patients with any kind of leukemia (acute and chronic). Normally, the granulocytic-erythroid ratio ranges from 2 to 4 : 1, but, in the setting of CML, cells of white lineage predominate and increments of any form of white blood cells, from myeloblasts to mature neutrophils, can be found. An increment in lymphocytes and red blood cell precursors is not characteristic of CML. The normal bone marrow cellularity is 50% fat and 50% or less cells, but, in the leukemias, the accelerated production of abnormal cells causes the fat to be replaced, and the cellularity increases to 100%. Finally, even in normal bone marrow, a very small number of blast cells can be found; in CML, a small percentage of blast cells can be found, but this does not necessarily signify acute leukemia. In blast crisis or acute leukemia, at least 20% of the cells in the bone marrow are blast cells.

- **What would be the most specific test for establishing the diagnosis of CML in this patient ?**

  The most specific test for establishing the diagnosis of CML is a cytogenetic investigation for the Ph^1 chromosome, which is found in 90% of cases of CML.

- **If the patient is started on single-agent chemotherapy, what would be the likely effect ?**

  The chemotherapeutic agent most commonly used in the treatment of CML is hydroxyurea. This therapy can improve the patient's quality of life by rapidly decreasing the number of white blood cells and platelets. It does not prolong survival very much, if at all, in patients with CML. The interferons can induce complete hematologic and cytogenetic remissions, with suppression of the Ph^1 chromosome in patients with CML. Most importantly tyrosine kinase inhibitors have high incidence of biologic responses and less toxicity. Allogeneic bone marrow transplantation has been the only curative treatment for CML but has a high rate of complications. Advanced age and the lack of suitable donors preclude its use in many patients, but it may be the therapy of choice in this 37-year-old man.

A 55-year-old man who is a smoker and has hypertension sees his internist because of malaise and nasal stuffiness with full sensation in his frontal sinuses. On further questioning, the patient also describes having itchy, red feet that worsen in the shower. The patient has no shortness of breath with activity and does not snore or experience daytime drowsiness.

Physical examination reveals a plethoric patient who is in no acute distress. His lungs are clear to auscultation. His liver span is 18 cm and his spleen tip is palpable. The following laboratory values are reported: hematocrit, 65%; white blood cell count, 8,500/mm^3; platelets, 210,000/mm^3; and differential: 50% segmented neutrophils, 30% lymphocytes, 3% basophils, and 10% monocytes.

Arterial blood gas determinations performed on room air reveal a partial pressure of oxygen of 65 mm Hg, a partial pressure of carbon dioxide of 38 mm Hg, and an oxygen saturation of 93%.

- What is the diagnosis in this patient?
- Why is it important to know whether the patient snores or experiences daytime drowsiness?
- What is the cause of this patient's nasal stuffiness?
- What should be the initial treatment in this patient?
- What is this patient's prognosis?

- **What is the diagnosis in this patient ?**

  This patient most likely has **polycythemia vera**. The oxygen saturation greater than 90% and the presence of splenomegaly support the diagnosis. The presence of mononuclear and basophilic cells also supports the diagnosis of a myeloproliferative disorder, which would be further supported by a bone marrow biopsy that shows trilinear hyperplasia.

- **Why is it important to know whether the patient snores or experiences daytime drowsiness ?**

  Snoring and daytime drowsiness are symptoms of sleep apnea, a cause of secondary erythrocytosis. Although phlebotomy can cure the patient's erythrocytosis, it cannot treat the nighttime hypoxia or sleep apnea, and the patient could go on to have right-sided heart failure.

- **What is the cause of this patient's nasal stuffiness ?**
  Although he may have a sinus infection, the nasal stuffiness is most likely due to increased blood viscosity.
- **What should be the initial treatment in this patient ?**
  Phlebotomy should be performed as soon as possible to decrease the hematocrit to 45% to 50%. The increased blood viscosity places this patient who has two other risk factors for atherosclerotic disease, namely smoking and hypertension, at risk for a stroke or cardiovascular accident.
- **What is this patient's prognosis ?**
  Even with careful treatment of his erythrocytosis with phlebotomy and chemotherapy, his life expectancy will probably be more limited because of his smoking and hypertension.

Hematology MCQ

1- A feature of idiopathic thrombocytopenic purpura common to both children and adults is

a. Occurrence after an antecedent viral illness
b. Absence of splenomegaly
c. Persistence of thrombocytopenia for more than 6 months
d. Necessity of splenectomy to ameliorate thrombocytopenia

2- Which one of the following is NOT a myeloproliferative disorder

a. CML
b. Polycythemia vera
c. Essential thrombocytopenia
d. Myeloid metaplasia

3- Normocytic normochromic anaemia is an expected feature of

a. beta-thalasaemia
b. chronic renal failure
c. iron deficiency anemia
d. alcoholic liver disease
e. myelodysplastic syndrome

4- All of the following are seen in intravascular hemolysis EXCEPT :

a. High urinary urobilinogen
b. Reticulocytosis
c. High plasma hemopexin
d. High urinary hemosiderin.

5- Auer rods are found in

a. Acute myeloid leukemia
b. Blast crises of chronic myeloid leukemia
c. Acute lymphoblastic leukemia
d. Blast crisis of chronic lymphoid leukemia

6- Which of the following does not produce iron overload in body

a. Chronic hemodialysis
b. Pernicious anemia
c. Alcoholic liver disease
d. Sideroblastic anemia

7- Anaphylactoid purpura may be associated with all EXCEPT

a. Joint pain
b. Proteinuria
c. Abdominal pain
d. Generalized lymphadenopathy
e. Urticarial maculopapular rash especially over buttocks & extensor surface of legs

8- The following are common clinical manifestations of leukemia EXCEPT

a. Fever
b. Pallor
c. Jaundice
d. Lymphadenopathy
e. Petechial hemorrhage

9- Which of the following anemias is associated with splenomegaly

a. Chronic renal failure
b. Aplastic anemia
c. Hereditary spherocytosis
d. Sickle cell anemia

10- In persons who have chronic myeloid leukemia, the translocation that accounts for the Philadelphia chromosome most commonly is found in

a. all cells of the body
b. all three hematopoietic cell lines but not in nonhematopoietic cells
c. all cells of the granulocytic cell line but not in nongranulocytic cells
d. all bone marrow stem cells but not in mature cells
e. all bone marrow stem cells and certain mature granulocytes

11- All of the following produce microcytic anemia EXCEPT

a. Sideroblastic anemia
b. Thalassemia
c. Pernicious anemia
d. Lead poisoning

12- The following are bad prognostic signs of acute leukemia EXCEPT

a. Leukocytosis > 50000/cmm
b. Mediastinal lymphadenopathy
c. Age < 2 & > 10 years
d. CNS manifestations
e. Hepatosplenomegaly

13- Mr Mamdouh is undergoing a hip replacement . During surgery he loses approximately 1 litre of blood and transfusion of 2 units of packed cells is commenced towards the end of the operation. The anaesthetist notices that his pulse has risen to 130/min and his blood pressure has fallen to 80/40 mmHg .He is noted to have frank hematuria. Which one of the following is the most likely cause of the sudden deterioration ?

a. Major ABO incompatibility
b. Myocardial infarction
c. Sepsis
d. Reaction to anaesthetic drug
e. Undetected blood loss

14- In a patient with chronic renal failure on replacement erythropoietin injections, which one of the following is NOT a recognized side effect of this treatment

a. Hypertension
b. Increased risk of thrombosis
c. Pure red cell aplasia
d. Anorexia & vomiting
e. Local pain at injection site

15- The most common type of anemia in Egypt is :

a. Thalassemia
b. Iron deficiency anemia
c. Sickle cell anemia
d. Aplastic anemia
e. Megaloblastic anemia

16- The normal reticulocytic count is

a. Less than 2%
b. 2 - 6%
c. 6 - 12%
d. 12 - 18%
e. 20 - 25%

17 - The mode of inheritance of thalassaemia is

a. Autosomal dominant
b. Autosomal recessive
c. Sex linked recessive
d. Sex linked dominant
e. None of the above

18- The normal bone marrow aspiration , blast cells not exceed

a. 1%
b. 5%
c. 10%
d. 20%
e. 28%

19 - Which of the following blood cells has the shortest blood half-life and is therefore most likely to become deficient as a result of chemotherapy treatment?

a. Red blood cells
b. Neutrophils
c. Megakaryocytes
d. Platelets

20 - Causes of huge spleen include all the following EXCEPT

a. Bilharziasis
b. Chronic malaria
c. Chronic myeloid leukemia
d. Hepatitis B

21- Therapy of haemophilia includes the following EXCEPT

a. Fresh blood
b. Fresh plasma
c. Fresh platelets
d. Factor VIII
e. DDAVP (Desmopressin)

22- Chloroma is found in

a. ALL
b. AML
c. CLL
d. CML

23- Non thrombocytopenic purpura is seen in all EXCEPT

a. Vasculitis
b. SLE
c. Chronic renal failure
d. Hereditary hemorrhagic telangietasis

24- A 35-year-old woman presents because of excessive bleeding after a dental extraction. She has a history of frequent prolonged menstrual periods, prolonged bleeding after the delivery of her only child 5 years ago, and easy bruisability. She also notes that her mother had a history of excessive bleeding as well. Physical exam at this time is unremarkable. The following studies are sent: WBC, 6500/cmm ; hematocrit, 39%; platelet count, 250,000/cmm ; PT, 12 sec ; PTT, 25 sec ; bleeding time, 15 min (*normal, 5 to 10 min*). The patient is taking no medicine and has taken no aspirin or nonsteroidal anti-inflammatory agents in the past month. Based on the available information, the most likely diagnosis is :

a. hemophilia A
b. hemophilia B
c. factor XII deficiency
d. von Willebrand's disease
e. Bernard-Soulier disease

25- Gum bleeding is characteristic of all EXCEPT

a. Chronic phenytoin therapy
b. Aplastic anemia
c. Scurvy
d. Hemophilia

26- Splenectomy is virtually curative in

a. G6PD deficiency
b. Thalassemia
c. ITP
d. Hereditary spherocytosis

27- Henoch-Schonlein purpura is not associated with

a. Thrombocytopenia
b. Palpable purpura
c. Acute diffuse GN
d. Abdominal pain

28- Red cell osmotic fragility is increased in

a. Thalassemia
b. Hereditary spherocytosis
c. Iron deficiency anemia
d. ITP

29- Hemolytic anemia is not produced by

a. Penicillin
b. Lithium
c. Methyl dopa
d. Quinidine

30- Cooley's anemia is

a. Sickle cell anemia
b. Megaloblastic anemia
c. Aplastic anemia
d. Thalassemia major
e. Iron deficiency anemia

31- Thrombocytopenia is absent in

a. DIC
b. Wiskott-Aldrich syndrome
c. Henoch-Schonlein purpura
d. Myelosclerosis

32- The outstanding feature of ITP is

a. Fever
b. Huge spleen
c. Gum bleeding
d. Sternal tenderness

33- Presence of anemia , jaundice & splenomegaly with increased MCHC is seen in

a. Liver cirrhosis
b. Thalassemia major
c. PNH
d. Hereditary spherocytosis

34- In polycythemia vera which is NOT true :

a. Low level of erythropoietin
b. High ESR
c. High serum vitamin B_{12} level
d. Increased RBC mass
e. Basophilia

35- Which isolated coagulation factor deficiency causes thrombosis

a. Factor V
b. Factor VII
c. Factor XI
d. Factor XII

36- Iron transport protein is

a. Transcobalamin II
b. Ferritin
c. Haptoglobin
d. Transferrin

37- Which of the following is false in haemophilia

a. Normal PT
b. Von Willebrand antigens level is grossly diminished
c. Increased PTT
d. Absent factor VIII coagulant activity

38- Esinophilia is a feature of

a. Non-Hodgkin's lymphoma
b. Sickle cell anemia
c. Hodgkin's lymphoma
d. Hemophilia

39- ↑ serum iron and ↓ iron binding capacity is a feature of

a. Chronic infection
b. Sideroblastic anemia
c. Alcohol liver disease
d. Thalassemia major

40- Best prognostic indicator in multiple myeloma is

a. Serum β_2 microglobulins
b. Bence Jones protein in urine
c. Number of plasma cells in marrow
d. Serum Ca level

41- Treatment of choice in hairy cell leukemia is

a. Chlorodeoxyadenosine
b. Cortisone
c. Splenectomy
d. Hydroxyurea

42- Tumor lysis syndrome produces all EXCEPT

a. Hyperuricemia
b. Hyperkalemia
c. Hypercalcemia
d. Hyperphosphatemia

43- Platelet transfusion is NOT indicated in

a. Aplastic anemia
b. Uremia with bleeding
c. DIC
d. Immunogenic thrombothytopenia

44- Best treatment in chronic myeloid leukemia is

a. Hydroxyurea
b. Allogenic bone marrow transplantation
c. Interferon
d. Radiotherapy

45- Autoimmune haemolytic anemia is associated with

a. ALL
b. AML
c. CLL
d. CML

46- Which of the following is contraindicated in polycythemia vera

a. Hydroxyurea
b. Chlorambucil
c. Interferon
d. Baby aspirin to prevent thrombosis

47- HAM test (acid serum test) is positive in

a. G6PD deficiency
b. Myelodysplastic syndrome
c. Paroxysmal nocturnal hemoglobinuria
d. Hemolytic uremic syndrome

48- Erythropoietin is secreted from all the following tumors EXCEPT

a. Renal cell carcinoma
b. Pheochromocytoma
c. Cerebellar hemangioblastoma
d. Oat cell carcinoma of the lung

49- Most sensitive & specific test for diagnosis of iron deficiency anemia is

a. Serum ferritin level
b. Percentage of transferrin saturation
c. Serum iron level
d. Serum transferrin receptor population

50- Half life of platelet is

a. 1 - 2 days
b. 3 - 4 days
c. 5 - 6 days
d. 7 - 8 days

51- Feature of sickle cell anemia do not include

a. Nocturia
b. Priapism
c. Hypersplenism
d. Leg ulcers

52- Pancytopenia may develop from all EXCEPT

a. Hemosiderosis
b. Paroxysmal nocturnal hemoglobinuria
c. Acute myeloblastic leukemia
d. Systemic lupus erythematosus

53- Which of the following is associated with prolonged bleeding time

a. Polycythemia vera
b. Von Willebrand's disease
c. Anaphylactoid purpura
d. Hemophilia

54- Peripheral blood picture is the most useful diagnostic aid in

a. Non Hodgkin's lymphoma
b. Multiple myeloma
c. Myelodysplastic syndrome
d. Chronic myeloid leukemia

55- Serum alkaline phosphatase level in multiple myeloma is usually

a. Low
b. Normal
c. High
d. Fluctuates

56- Coagulation factor deficient in stored blood is

a. VII
b. V
c. IX
d. II

57- Half life of albumin is

a. 1 - 2 days
b. 10 - 14 days
c. 16 - 20 days
d. 20 - 26 days

58- Life span of platelets is

a. 2 - 4 days
b. 5 - 7 days
c. 9 - 11 days
d. 13 - 15 days

59- Megakaryocytosis in bone marrow is seen in all EXCEPT

a. Myeloid metaplasia
b. Polycythemia vera
c. Chronic myeloid leukemia
d. ITP

60- Parahemophilia is deficiency of factor

a. IX
b. V
c. XI
d. VIII

61- A 55-year-old man with type 1 diabetes undergoes dialysis three times a week for end-stage renal disease. You recently started him on erythropoietin injections for chronic anemia (hematocrit, 25%).
Which of the following is the best test to determine whether this patient will respond to the erythropoietin treatment?

a. Erythropoietin level
b. Hematocrit
c. Creatinine level
d. Reticulocyte count
e. Blood urea nitrogen

62- A 34-year-old woman undergoes chemotherapy for advanced-stage breast cancer. As expected, she develops pancytopenia. Which cell line would you expect to be the last to recover in this patient?

a. Eosinophils
b. Platelets
c. Basophils
d. Monocytes
e. RBCs

63- A 60-year-old man presents with complaints of headache, light-headedness, blurry vision, and fatigue; these symptoms have been increasing over the past month. He reports that he has felt weak and has not had much energy. He also reports generalized itching, which usually occurs after he takes a hot shower. Physical examination reveals facial plethora. His spleen is palpable 2 cm below the left costophrenic angle. Laboratory results reveal the following: Hb, 18; Hct, 61; platelets, 500,000; leukocytes, 17,000. Which of the following is the most appropriate diagnosis for this patient?

a. Gaisböck syndrome (relative polycythemia)
b. Pickwickian syndrome
c. Polycythemia vera
d. Acute myeloid leukemia
e. Chronic myeloid leukemia

64- A 59-year-old woman with severe, progressive rheumatoid arthritis is found to have a neutrophil count of 1,200/mm³ on routine hematologic testing. She takes methotrexate and prednisone for her rheumatoid arthritis. In addition to rheumatoid nodules and rheumatoid joint deformities, moderate splenomegaly is noted on physical examination. Which of the following would not be contributing to this patient's neutropenia ?

a. Methotrexate
b. Corticosteroids
c. Antineutrophil antibodies
d. Felty syndrome

Answers

1- b
2- c
3- b
4- c
5- a
6- b
7- d
8- c
9- c
10- b
11- c
12- e
13- a
14- d
15- b
16- a
17- b
18- b
19- b
20- d
21- c
22- b
23- b
24- d
25- a
26- d
27- a
28- b
29- b
30- d
31- c
32- c
33- d
34- b
35- d
36- d
37- b
38- c
39- b
40- a
41- a
42- c
43- d
44- b
45- c
46- b
47- c
48- d
49- a
50- b
51- c
52- a
53- b
54- d
55- b
56- b
57- d
58- c
59- c
60- b
61- d
62- b
63- c
64- b

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